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ABSTRACTS OF WORLD MEDICINE

It is the aim of this journal to provide the reader with abstracts of all important articles appearing in medical periodicals published in every part of the world, and in this way to enable him to keep in touch with new developments throughout the whole field of medicine and in each of its special branches, including those aspects of surgery which are of particular concern to the physician.

More than 1,600 periodicals are surveyed, from which are selected for abstracting those papers which appear to make some useful contribution to the sum of medical knowledge or experience. Each paper is abstracted in sufficient detail to indicate to the general reader the nature and value of that contribution and to enable the specialist to assess its importance in relation to his own work and to decide whether the original article should be read in full. The author's own summary or an editorial summary published with the original article may occasionally be reproduced if it is suitable for these purposes, and the title and reference alone may be published in order to draw attention to a review article or other type of paper which cannot readily be abstracted.

The abstracts in each issue are grouped in sections according to subject and, so far as possible, those dealing with medical and surgical aspects of the same problem appear together. The titles of papers written in languages other than English are given both in translation and in the original form. The titles of journals are given in full and also abbreviated according to the rules adopted in the *World List of Scientific Periodicals*, as modified by *ISO Recommendation R4: International Code for the Abbreviation of Titles of Periodicals* (International Standards Organization, 1957), and in *World Medical Periodicals* (Second Edition, World Medical Association, 1957). The transliteration of authors' names from the Cyrillic alphabets is in accordance with *ISO Recommendation R9: International System for the Transliteration of Cyrillic Characters* (International Standards Organization, 1955).

Explanatory or critical comments by the abstracter or editor are enclosed within square brackets.

ABSTRACTS OF WORLD MEDICINE

VOL. 30 NO. 5 NOVEMBER, 1961

Pathology

1084. **Experimental Poliomyelitis following Intramuscular Virus Injection. I. The Effect of Neural Block on a Neurotropic and a Pantropic Strain**

N. NATHANSON and D. BODIAN. *Bulletin of the Johns Hopkins Hospital* [*Bull. Johns Hopk. Hosp.*] **108**, 308–319, May, 1961. 29 refs.

In the 65 cases of paralytic poliomyelitis which occurred in the Cutter incident in 1955 among 400,000 persons following intramuscular inoculation of poliomyelitis vaccine containing residual virulent virus a high incidence of initial involvement in the inoculated extremity was observed. This could be accounted for by postulating either a direct spread by a neural route or invasion of the central nervous system via the blood stream with localization due to a provoking effect of the injection. This paper presents the results of intramuscular poliovirus injection in cynomolgus monkeys with a neurotropic and a pantropic strain, neural spread being blocked by freezing the nerve innervating the injected muscle.

Following intramuscular injection of a large inoculum of the highly neurotropic MV (Type 2) strain, paralysis developed in 25 out of 26 animals, initially in the inoculated limb in 21, but in 11 animals subjected to neural block just before injection of the virus no paralysis developed. In these animals antibody titres ranging from 1:8 to 1:1,000 were nevertheless found 3 to 7 weeks later. By contrast, after intramuscular injection of the pantropic Mahoney (Type 1) strain neural block gave no protection, paralysis developing in almost all the animals. There was some evidence of initial localization in the injected extremity, presumably due to the provoking effect.

The findings of this and other studies suggest that a high frequency of initial paralysis in the inoculated extremity as seen in the Cutter incident, which was associated with the Mahoney strain, may occur as a result of an increase in the influence of the provoking effect when the paralytic attack rate is low.

A. Ackroyd

1085. **Experimental Poliomyelitis following Intramuscular Virus Injection. II. Viremia and the Effect of Antibody**

N. NATHANSON and D. BODIAN. *Bulletin of the Johns Hopkins Hospital* [*Bull. Johns Hopk. Hosp.*] **108**, 320–333, May, 1961. 2 figs., 38 refs.

After intramuscular injection of a large inoculum of Mahoney-strain poliovirus massive viraemia developed rapidly and fell off rapidly in cynomolgus monkeys with no pre-antibody, but after a smaller inoculum was injected viraemia appeared more gradually, was present in almost all animals on Days 3 and 4, and waned slowly, not disappearing until Day 10. Peak titres about Day 3 were slightly higher after the smaller inoculum. Variations in the parameters of viraemia were influenced not only by the size of the inoculum, but also by individual variability. Viraemia was one of the factors which determined sites of initial paralysis and also the incubation period—the more delayed the onset of viraemia, the more caudal the initial site, and the greater the interval between virus injection and appearance of viraemia, the longer the incubation period.

Homologous antibody which developed between Days 3 and 9 appeared to be responsible for the waning and termination of viraemia, although this is not the case when viraemia is moderate or minimal.

In some animals with pre-existing active immunity to a heterologous virus type (Type 2) partial protection against paralysis was observed. This was probably related to damping of viraemia due to neutralization of much of the challenge virus by pre-antibody present at very low levels rather than to the occurrence of a precocious antibody response.

In these experiments the incubation period before the development of paralysis could be broken down into 3 components: multiplication at the peripheral site, 1 to 2 days; onset of viraemia to invasion of the central nervous system, 1 day; and incubation within the central nervous system, 5 to 6 days. Factors which have an important influence on each component are: virus inoculum; growth characteristics of the virus strain; and the specific peripheral or central locus within which the virus is multiplying.

A. Ackroyd

1086. **Relationship of Increased Histidine Decarboxylase Activity to *Bordetella pertussis* Vaccine Sensitization of Mice**

R. W. SCHAYER and O. H. GANLEY. *Journal of Allergy* [*J. Allergy*] **31**, 204–213, May–June, 1961. 1 fig., 27 refs.

The authors, at the Merck Institute of Therapeutic Research, Rahway, New Jersey, have investigated the increase in histidine decarboxylase activity which occurs in mice after the injection of pertussis vaccine. The histidine decarboxylase activity in mouse lung was determined according to a method published earlier (*Amer. J. Physiol.* 1959, **196**, 295). Mice were injected with pertussis vaccine and their subsequent sensitivity to intravenous injection of serotonin, intraperitoneal injection of histamine, and intravenous injection of egg albumen (the last after previous passive sensitization) was investigated. It was found that the histidine decarboxylase activity reached its peak 3 to 4 days after the injection of pertussis vaccine. At about the same period the response to histamine, serotonin, anti egg albumen also reached its maximum. The decrease in these responses also ran approximately parallel to the decrease in decarboxylase

activity. The output of corticosterone increased immediately after the injection of pertussis vaccine, but this increase lasted only up to 16 hours, so that it could not protect the animals later on.

It is suggested that the pertussis sensitization is caused by an increase in newly synthesized histamine and its influence on certain cells of lung or other tissue.

H. Herxheimer

1087. **Experimental Eosinophilia. III. Regional Lymph Node Responses to Reactions of Tissue Sensitization**
S. G. COHEN, M. KANTOR, and L. GATTO. *Journal of Allergy* [*J. Allergy*] **31**, 214–222, May–June, 1961. 2 figs., 23 refs.

"The occurrence of eosinophilic granular cell responses within regional lymph nodes draining passively sensitized cutaneous sites formed the basis for this investigation", which is reported from the Veterans Administration Hospital and the Department of Biology, Wilkes College, Wilkes-Barre, Pennsylvania. Bovine serum albumin and corresponding antiserum were injected into the rabbit foot-pad, and the popliteal lymph nodes examined histologically 4 hours later. The maximum eosinophilic infiltration of the lymph nodes was found when the antiserum was injected 30 minutes after the antigen. There was no response if antigen or antiserum was injected alone, or after the injection of histamine or heparin. Antihistamines and antiserotonins did not modify the eosinophilic response. *H. Herxheimer*

1088. **Leucocyte Migration from Small Blood Vessels Stimulated with Ultraviolet Light: an Electronmicroscope Study**
H. W. FLOREY and L. H. GRANT. *Journal of Pathology and Bacteriology* [*J. Path. Bact.*] **82**, 13–17, 1961. 25 figs., 2 refs.

The authors, working at the Sir William Dunn School of Pathology, Oxford, have used the rabbit ear-chamber technique to study the emigration of leucocytes from small vessels, as provoked by exposure to ultraviolet rays. After an appropriate stimulus tissue fixation was begun *in vivo*, followed by excision of the tissue and further fixation *in vitro*.

In electron-microscopic studies (illustrated by a large series of superb photographs), polymorphs were seen to adhere to the endothelium. No morphological cause to account for this phenomenon was observed. The side of the polymorph in contact with endothelium became flattened. Pseudopodia coming from the polymorphs were seen to cause indentations in the endothelium and to force a passage through it, sometimes pushing the endothelium aside over a wide area. When the polymorph reached the basement membrane it began to move parallel to, but outside, the endothelium until finally escaping through gaps among the surrounding fibres and cells to reach the tissue spaces. Monocytes were observed to behave similarly, while no lymphocytes or eosinophils were seen. The cytoplasm of the endothelial cells in some cases contained large vacuoles filled with dense material, other endothelial cells having smaller vacuoles filled with fine granules.

The findings substantially agree with those of Marchesi and Florey (*Quart. J. exp. Physiol.*, 1960, **45**, 343) when working with rat mesentery. [See also *Abstr. Wld Med.*, 1961, **30**, 265.] *G. Loewi*

CHEMICAL PATHOLOGY

1089. **Determination of Gastric Acidity by Measurement of Azure A in the Blood Serum**
H. L. SEGAL and R. P. PLOSSCOWE. *American Journal of Digestive Diseases* [*Amer. J. dig. Dis.*] **6**, 485–491, June, 1961. 5 figs., 2 refs.

Further data are presented on a method of tubeless gastric analysis based on measurement of the azure-A level in the blood serum after the ingestion of an azure A resin compound. This method has been previously reported by the authors (*J. Lab. clin. Med.*, 1960, **55**, 815) and is a development of the original method in which the excretion of azure A in the urine was estimated (Segal *et al.*, *Gastroenterology*, 1955, **28**, 402; *Abstr. Wld Med.*, 1955, **18**, 350). A study of the one-hour serum azure-A level in 200 individuals whose gastric acidity was determined by the usual method of tubeless gastric analysis revealed 20 false negative results in 147 acid secretors (13·5%) and one false positive result in 53 achlorhydric individuals (1·9%). A repeat examination of the serum azure-A level indicated the presence of free gastric acid in 10 out of 12 patients in whom a false negative result had originally been obtained. This reduced the inconsistencies to about 7%. A comparison of the one-hour serum azure-A levels with the *p*H of the gastric aspirate in 68 individuals revealed 3 false negative results among the 45 acid secretors (6·6%) and 2 false positive results among the 23 achlorhydrics (9%). A repeat test on the 3 individuals with false negative results revealed the presence of acid. Comparison of the one-hour and 1½-hour serum azure-A levels in 14 acid secretors and 6 achlorhydrics indicated that measurement at 1½ hours results in a significant number of inconsistencies.

The results show that measurement of azure A in the serum instead of the urine can be used to determine the presence or absence of free gastric acid by the tubeless method of gastric analysis, but it is not recommended as a routine procedure because it is more complicated to perform than the urine test. If, however, the laboratory facilities necessary for determining serum azure-A levels are available any errors resulting from incorrect urine collection may be avoided. *S. M. Hardy*

1090. **A Study of Six Representative Methods of Plasma Bilirubin Analysis**
D. WATSON and J. A. ROGERS. *Journal of Clinical Pathology* [*J. clin. Path.*] **14**, 271–278, May, 1961. 33 refs.

This paper from the Royal Women's Hospital, Melbourne, reports a comparison of 6 different methods used for the estimation of bilirubin in the plasma. They included a spectrophotometric technique and 5, diazo coupling procedures. In some of these last 5, coupling was carried out in the absence, and in some in the pre-

sence, of alcohol; some involved removal of protein by precipitation and some did not. It was noteworthy that the presence of haem pigment caused underestimation of bilirubin in some cases and overestimation in others and that techniques which involved the precipitation of protein were liable to give results which were too low. Direct spectrophotometry was satisfactory so long as the amounts of conjugated bilirubin were not too high. The authors conclude that the method of Lathe and Ruthven (*J. clin. Path.*, 1958, **11**, 155) is the most suitable and reliable. In this technique coupling takes place in 50% methyl alcohol and protein is not precipitated.

H. Lehmann

1091. **Multiple Plasma Enzyme Activities in Liver Disease**

T. HARGREAVES, I. JANOTA, and M. J. H. SMITH. *Journal of Clinical Pathology* [*J. clin. Path.*] **14**, 283–288, May, 1961. 1 fig., 12 refs.

Working at King's College Hospital Medical School, London, the authors have investigated the question whether the measurement of the activity of various enzymes in plasma from random blood samples from patients with hepatic diseases would reveal patterns of abnormality characteristic of particular disorders of the liver. The 53 patients studied were suffering from infective hepatitis (7), obstructive jaundice (25), hepatic cirrhosis (12), and neoplastic conditions involving the liver (9). The clinical diagnosis was confirmed at biopsy, operation, or necropsy in 41 cases and by the results of various liver function tests in the remainder. Random specimens of blood were obtained from all the patients and serial samples in selected cases. The plasma enzymes measured were: glutamic–oxalacetic and glutamic–pyruvic transaminases, aldolase, pseudocholinesterase, and *iso*citric, lactic, and phosphogluconic dehydrogenases.

The conclusion was reached that there were no consistent patterns which would help in the differential diagnosis of hepatitis, obstructive jaundice, cirrhosis, and liver tumours. For example, the claim that the plasma *iso*citric dehydrogenase level is usually normal in cases of extrahepatic obstruction could not be confirmed and in fact it was found to be raised in 30% of such cases. The authors state that the thymol turbidity test is much more useful for the differentiation of acute hepatitis from post-hepatitic jaundice. On the other hand serial measurements of multiple plasma enzyme activities give much useful information concerning the course of a particular liver disorder. The authors do not suggest that it is necessary to measure all the enzyme activities listed above; in their experience changes in the activity of either of the two transaminases are representative of the major changes in activity of the other enzymes.

H. Lehmann

1092. **The Measurement of Urine Chloride as a Test of Renal Function**

R. P. LYON. *Journal of Urology* [*J. Urol.* (*Baltimore*)] **85**, 884–888, June, 1961. 4 figs., 3 refs.

The limitations of specific gravity measurement and of the phenolsulphonphthalein (PSP) test and the advantages of the urine chloride test in the assessment of renal function in patients with oliguria are discussed in this paper from the University of California School of Medicine, San Francisco. Scribner's urine chloride test (*Proc. Mayo Clin.*, 1950, **25**, 209; *Abstr. Wld Med.*, 1950, **8**, 369) is recommended for routine bedside use. Measurement of specific gravity is of no value as an indication of renal function after the onset of uraemia when hydration is within normal limits; the PSP test becomes unsatisfactory when acute reversible failure occurs. At this point a comparison of urine chloride and serum chloride levels helps to distinguish between organic and physiological lesions. Less than 30 mEq. or more than 100 mEq. of chloride per litre of urine suggests that lower nephron nephrosis is absent and that the lesion has a physiological as well as an organic basis; repair of the renal lesion is achieved by administration of fluids and electrolytes. Tubular lesions associated with 40 to 100 mEq. of chloride per litre of urine usually repair rapidly, suggesting that the lesions are incomplete.

Four case reports are included to illustrate the usefulness of urine chloride measurement in diagnosis and treatment.

J. E. Page

1093. **Lactic Dehydrogenase Activity in Cancer Diagnosis.** [Review Article]

F. WRÓBLEWSKI. *Medical Clinics of North America* [*Med. Clin. N. Amer.*] **45**, 513–520, May, 1961. 5 figs., 16 refs.

HAEMATOLOGY

1094. **Mechanism and Significance of Erythrocyte Sedimentation Rate**

G. RUHENSTROTH-BAUER. *British Medical Journal* [*Brit. med. J.*] **1**, 1804–1806, June 24, 1961. 4 figs., 14 refs.

The author of this paper from the Max Planck Institute for Biochemistry, Munich, states that an increase in the blood fibrinogen or gamma-globulin fractions is only coincidental to a high erythrocyte sedimentation rate and not its cause. Fractionation of normal and high-sedimenting plasmas by means of ammonium sulphate precipitation or preparative paper electrophoresis has shown that the phenomenon is caused by specific proteins. By both methods protein fractions could be obtained which, at a concentration of 1 to 2%, caused a high sedimentation rate provided supplements such as 0·6% dextran had been added. The supplements by themselves had no effect, the proteins which produced the increased sedimentation rate behaving, therefore, like incomplete antibodies.

The term "agglomerin" is proposed for all plasma proteins which, on the addition of supplement, cause an increase in sedimentation rate. In this respect fibrinogen is an agglomerin which is always present in blood. The agglomerins of different patients are not always found in the same electrophoretic fraction, but may be present in more than one globulin fraction in one patient.

All plasmas contain a pro-inhibitor of sedimentation which is activated at body temperature by a specific lipase, one of the so-called B group of esterases. Erythrocytes yield a glucolipid fraction containing the sub-

stance which combines with the agglomerins. Almost all anti-inflammatory substances—for example, salicylates, cinchophen, phenylbutazone—are strong inhibitors of agglomerins. Cortisone is a partial inhibitor.

It is suggested that agglomerin production is stimulated by breakdown material from either homologous or heterologous (bacterial) cells acting on plasma cells and that agglomerins are involved in the inflammatory response, the action on erythrocytes being only coincidental. *H. Caplan*

1095. **The Correction of the Westergren Sedimentation Rate Using Heparinized Blood**
T. H. NEWMAN and R. L. WATERFIELD. *Guy's Hospital Reports* [*Guy's Hosp. Rep.*] **110**, 128–133, 1961. 2 refs.

It is pointed out that the physical factors which determine the sedimentation rate of erythrocytes (E.S.R.) are: (1) the size of the particles falling, (2) the concentration of the particles, (3) the difference in specific gravity between the particles and the suspending fluid, and (4) the viscosity of the suspending fluid. The two most important are the tendency to form rouleaux and a diminished concentration of erythrocytes in the plasma, both of which increase the E.S.R. The outstanding cause of increased rouleaux formation is a rise in either the fibrinogen or the globulin content of the plasma; a rise in the albumin content and gross abnormality in the shape of the erythrocytes have the opposite effect. A greatly increased blood cholesterol level can also produce a raised E.S.R. Thus the E.S.R. as ordinarily determined is a measurement of the resultant effects of two completely different sets of factors—one depending on the composition of the plasma and the other on the concentration and nature of the erythrocytes. In the Westergren method of determining the E.S.R., which gives the most consistent results, the blood is diluted with liquid anticoagulant so that correction for anaemia is more difficult than in the Wintrobe method, in which a solid anticoagulant is used.

The present authors report the use of heparinized blood so that the cell volume can be corrected before mixing with the citrate solution in the Westergren method. Duplicate measurements with ordinary and heparinized venous blood covering a wide range of sedimentation rates and a wide range of percentage cell volumes showed identical results. Samples of blood were then obtained from anaemic and polycythaemic patients and mixed with dried heparin (approximately 10 units per ml.); the percentage cell volume was determined. An accurately measured volume of the sample was then pipetted into a centrifuge tube, spun gently, and the volume of plasma calculated from the percentage cell volume to bring the sample to a normal percentage cell volume removed or added. Finally, 4 parts of the corrected sample were mixed with one part of a 3·8% solution of sodium citrate in the ordinary way and the Westergren tube was set up. Curves were drawn to give the correction to be applied for a given cell volume and a given sedimentation rate and these provided a reliable figure for the corrected E.S.R. provided the anaemia or polycythaemia was not too severe. The authors point out that this technique for correcting the Westergren value for the E.S.R. in anaemia or polycythaemia is valid only when the erythrocytes are morphologically normal. Even in anaemic patients a streaky blood film indicates that the E.S.R. is raised.
A. Ackroyd

1096. **Thromboplastin Generation Accelerator, a Newly Recognized Component of the Blood Coagulation Mechanism Present in Excess in Certain Thrombotic States**
C. A. PASCUZZI, J. A. SPITTEL JR., J. H. THOMPSON JR., and C. A. OWEN JR. *Journal of Clinical Investigation* [*J. clin. Invest.*] **40**, 1006–1018, June, 1961. 2 figs., 27 refs.

MORBID ANATOMY AND CYTOLOGY

1097. **Non-suppurative Lesions in Staphylococcal Septicaemia**
D. E. B. POWELL. *Journal of Pathology and Bacteriology* [*J. Path. Bact.*] **82**, 141–149, 1961. 13 figs., 26 refs.

The author, writing from the Welsh National School of Medicine, Cardiff, reports necropsy findings in 40 cases of staphylococcal septicaemia, all of which showed metastatic suppurating foci. The non-suppurating lesions only are described here. With regard to the kidney, 2 cases showed bilateral necrosis with fibrin-staining thrombi in small vessels. In another 14 cases there was patchy tubular damage with lesions in associated vessels. Two cases showed peripheral infarcts. Glomerulonephritis was diagnosed in 16 cases on a basis of proliferation of the glomerular tuft cells, with or without exudate in the capsular space. Crescent formation was sometimes observed. Focal embolic nephritis was diagnosed 8 times. The author regards vascular involvement as the basic renal lesion. Fibrinoid changes were commonly seen with arterial, venous, or capillary thrombi in 30 cases.

Thrombosis of major vessels was found in the lung at 13 necropsies; in 11 of these a vein was occluded and some of the thrombi were infected. Thrombosis of the smaller vessels was associated with fibrinoid necrosis and focal haemorrhages. The brain showed some evidence of vascular involvement. Liver lesions were seen twice, splenic infarcts 9 times, and focal adrenal cortical necrosis 4 times. The clinical significance of these lesions is discussed. The author considers the possibility of the existence of a hypersensitivity state similar to the Shwartzman phenomenon. [This would be unlikely to involve the larger vessels.] *G. Loewi*

1098. **A Morphologic and Histochemical Analysis of the Human Jejunal Epithelium in Nontropical Sprue**
H. A. PADYKULA, E. W. STRAUSS, A. J. LADMAN, and F. H. GARDNER. *Gastroenterology* [*Gastroenterology*] **40**, 735–765, June, 1961. 37 figs., bibliography.

In this study [carried out at Harvard Medical School and the Peter Bent Brigham Hospital, Boston] an attempt was made to define the structural and histochemical properties of the human intestinal epithelium in nontropical sprue and to interpret these findings in terms of

the known biologic facts concerning the origin, migration, and differentiation of the normal intestinal epithelium. Isotopic marking of the normal intestinal epithelium has demonstrated conclusively that cells originate in the crypts, migrate along the villus, and are extruded at the apex of the villus. Histochemical and electron microscopic studies were made on mucosal biopsies of the jejunum obtained by intraluminal biopsy capsule from the following three groups of fasted individuals: (1) 13 patients with diagnoses of the nontropical sprue, (2) 2 healthy physicians, and (3) 24 persons with various abnormalities but, nevertheless, normal mucosae. Mitotic activity of the normal and abnormal epithelia were estimated by counts of dividing cells in the crypts and also in the whole epithelial population.

The jejunal epithelium of nontropical sprue has three distinct zones. Histologically, long distended "crypts" open onto a flat luminal surface. Histochemically, the apparent crypt can be differentiated into two zones: (1) a basal region (zone 1) of small germinative cells which lack phosphatases, have low esterase and succinic dehydrogenase, and form the counterpart of the normal crypt; (2) the upper part (zone 2), which has taller cells with the histochemical and cytologic properties of normal villus cells. This zone has the rich complement of phosphatases, esterase, and succinic dehydrogenase which typifies absorptive cells. Thus, from these findings, the upper part of the apparent crypt in sprue corresponds histochemically to part of the villus in the normal. At the mouth of the crypts, there is an abrupt junction of the normal appearing villous cells of zone 2 with the unique epithelium which covers the flat surface. These luminal cells (zone 3) have a pseudo-stratified appearance, and their cytoplasm is strongly basophilic. Most of this basophilia is attributable to ribonucleoprotein. This surface epithelium, which sharply reflects the abnormal alteration of the villus, is clearly deficient in succinic dehydrogenase, esterase, acid phosphatase, and adenosine triphosphatase activities. Of the enzymes studied, only alkaline phosphatase seems undiminished in the surface epithelium (zone 3). Thus, the villus in nontropical sprue is composed of a fairly normal epithelium which is invaginated (zone 2) and a surface epithelium (zone 3) which exhibits profound chemical and structural deviations from the normal. From this histochemical zonation in sprue, it is suggested that there is a disturbance in the differentiation of the epithelium.

With the electron microscope, absorptive cells which showed abnormalities in the mitochondria and microvilli are frequently observed. These mitochondria are larger and more rounded or oval; the matrix is often less dense than normal. The microvilli are often shorter and fewer in number. The membranous components of the endoplasmic reticulum are less abundant. The Golgi complex is normal.

The rate of cell loss and cell renewal in sprue is significantly increased. This interpretation is based on the greater mitotic activity in the crypts and in the 2-fold elevation in the mean mitotic index of the complete intestinal epithelium. In addition, in sprue, the crypts are twice as long, and mitotic figures are frequently seen on the villi.

An attempt is made to relate the above findings to the etiology and the impaired intestinal absorption in sprue. —[From the authors' summary.]

1099. **Exfoliative Cytology in Gastric Malignancy: with Special Reference to the Diagnostic Significance of Nuclear Size and Mitotic Frequency.** [Monograph, in English]
K. Seppälä. *Acta medica Scandinavica* [*Acta med. scand.*] **169**, Suppl. 363, 1–79, 1961. 20 figs., bibliography.

1100. **The Incidence of Atherosclerosis in Post-mortem Examinations in Leningrad during the Period 1954–8.** (Заболевание атеросклерозом по секционным данным Ленинграда за 1954–1958 гг.)
P. V. Sipovskii and Z. A. Vlasova. *Клиническая Медицина* [*Klin. Med.* (*Mosk.*)] **39**, 65–73, May, 1961.

This study of the incidence of atherosclerosis is based on 15,616 post-mortem examinations carried out in various medical institutions in Leningrad during the period 1954–8 on subjects aged from 30 to over 80 years. In 1,044 cases (6·7%) the atherosclerosis was the principal cause of death, while in a further 2,940 cases it was a concomitant cause. An accompanying table shows that the incidence of atherosclerosis increased with each decade of age.

In cases in which atherosclerosis was the principal disease the most frequent complications were chronic cardiac insufficiency, myocardial infarction, and vascular lesions of the central nervous system. As a concomitant affection, atherosclerosis was usually present in patients with gall-bladder disease, pancreatitis, diabetes, and chronic non-specific diseases of the lungs. Its incidence was lower in those with peptic ulcer or pulmonary tuberculosis. *A. Orley*

1101. **Atherogenesis and Plasma Constituents**
R. H. More and M. D. Haust. *American Journal of Pathology* [*Amer. J. Path.*] **38**, 527–537, May, 1961. 12 figs., 22 refs.

A study is reported from Queen's University and Kingston General Hospital, Kingston, Ontario, of the developmental relationship between atheroma and deposits of blood proteins on or into the arterial wall. The material consisted of 130 out of 1,300 sections of arteriosclerotic lesions from 150 aortas and the coronary arteries of 100 hearts.

When the mural thrombus was small or the insudation into the intima superficial all the blood protein substance was commonly converted to connective tissue elements by means of avascular organization progressing from the lumen. When the thrombi were large this avascular organization co-existed with organization from the base of the thrombi with capillaries growing in from the media. The organization by these two processes was sometimes complete, but frequently remnants of fibrin remained between the two types of organization. In addition, unorganized fibrin was present at the base of young connective-tissue plaques. Fibrin remnants were also found deep in the serofibrinous insulate within the intima. Lipophages appeared in early insudative and thrombotic lesions and were numerous in advanced

lesions. In more advanced lesions the lipophages disintegrated, thus becoming the nidus for atheroma. It was clear that intracellular and extracellular lipids accumulated as the fibrin and other plasma constituents disappeared.

The authors state that these observations establish the sequential relationship between the accumulation of blood proteins in and on the intima and the genesis of atheroma. [There is no information, however, on the factors which promote this sequence nor any indication why one mass of intimal protein was completely organized, while in another this was only partially accomplished with resultant atheroma formation.] *H. Caplan*

1102. **Coronary Arterial Calcification: a Review**
D. H. BLANKENHORN. *American Journal of the Medical Sciences* [*Amer. J. med. Sci.*] **242**, 1–10, July, 1961. 2 figs., 28 refs.

1103. **An Assessment of the Anatomical Factor in Cor Pulmonale in Emphysema**
M. S. DUNNILL. *Journal of Clinical Pathology* [*J. clin. Path.*] **14**, 246–258, May, 1961. 14 figs., 35 refs.

An attempt has been made at the Radcliffe Infirmary, Oxford, to assess the anatomical factors concerned in the pathogenesis of the syndrome of chronic bronchitis and emphysema, and the present paper reports the findings in the pulmonary vessels in 44 cases examined post mortem. The thickness of the myocardium of the right and left ventricles was measured and the lungs were injected with a barium sulphate mixture through the pulmonary artery. Slices of lung were examined by x-ray photography.

The presence of precapillary broncho-pulmonary arterial anastomoses was demonstrated in all cases with localized areas of bronchiectasis. While intimal fibrosis, distortion of the pulmonary vascular bed by areas of fibrosis, or thrombosis of vessels may cause some decrease in the pulmonary vascular bed, the author considers the main cause of pulmonary back pressure and cor pulmonale to be the presence of emphysema. In these cases the vessels run round the edges of the bullae and are subjected to various extravascular pressures.

J. B. Wilson

IMMUNOPATHOLOGY

1104. **Variations in the Morphological Patterns of "Autoimmune" Nuclear Fluorescence**
J. S. BECK. *Lancet* [*Lancet*] **1**, 1203–1205, June 3, 1961. 3 figs., 11 refs.

In many collagen diseases the serum contains antibodies to nucleoprotein. One way of detecting these is to treat sections of mammalian liver with the serum followed by fluorescein-labelled rabbit anti-human γ globulin, when the nuclei in the section become fluorescent. The author, working at the National Institute for Medical Research, London, examined sera from 30 cases of various types of collagen disease, including Sjögren's syndrome, lupus erythematosus, acrosclerosis, rheumatoid arthritis, and dermatomyositis. He found three different patterns of staining. (1) Homogeneous nuclear staining was found in 14 of the 30 cases. The responsible antigen was removed by deoxyribonuclease and it was identified as nucleohistone by absorption and *in vitro* staining experiments. (2) Speckled nuclear staining occurred with 16 of the sera. The antigen, which was not identified, was soluble in physiological saline and was possibly a protein. (3) Nucleolar staining, associated with homogeneous nuclear staining, occurred with the serum from one case of Sjögren's syndrome. The antigen was removed by ribonuclease, but the antibody was not absorbed by ribonucleoprotein *in vitro*. The antigen was possibly a ribonucleic acid immunologically distinct from cytoplasmic ribonucleic acid. *M. C. Berenbaum*

1105. **Studies on Leucocyte Iso- and Auto-antibodies**
C. P. ENGELFRIET and J. J. VAN LOGHEM. *British Journal of Haematology* [*Brit. J. Haemat.*] **7**, 223–238, April, 1961. 40 refs.

In this investigation, carried out at the Central Laboratory of the Netherlands Red Cross Blood Transfusion Service, Amsterdam, leucocyte isoantibodies and autoantibodies (clearly and precisely defined) were sought for by an agglutination test in which a slight modification of the technique of Dausset *et al.* was used and by the antiglobulin consumption test (A.C.T.). Sera were obtained from patients who had received multiple transfusions, patients with leucopenia, patients with disseminated lupus erythematosus, and also from pregnant women.

Sera from one-third of the patients (350) who had received multiple transfusions contained leucocyte isoantibodies, but the majority of these were of the incomplete variety. The authors state that the presence of these antibodies is an important cause of non-haemolytic transfusion reactions characterized by fever and rigors. Leucocyte antibodies of rather low titre were found in sera from 15 out of 838 pregnant women. It appears they can be produced by pregnancy immunization and were slightly more common in the sera of patients with an obstetrical history, stillbirths, abortions, and children with haemolytic disease than in those whose history was normal. [Unfortunately no information is given of any investigations of the outcome of the pregnancies in which the leuco-agglutinins were found.]

The A.C.T. was carried out on sera from 83 patients with clinical disseminated lupus erythematosus (D.L.E.) or rheumatoid arthritis accompanied by a positive reaction to the L.E. test. In all except one, a positive response to the A.C.T. was obtained. Some evidence is available to suggest that the A.C.T. is more sensitive than the indirect L.E. test. It is suggested that sensitization of leucocytes *in vivo* probably does not occur in patients with D.L.E. On the other hand in all of 35 cases of leucopenia due to other causes autoantibodies were found; the authors state that sensitization *in vivo* in these cases is apparently the rule, but the significance is still uncertain.

[The details of the methods used are worthy of consultation.] *I. Dunsford*

Microbiology and Parasitology

1106. **Identification of Poliovirus Isolates with Fluorescent Antibody**
M. H. HATCH, S. S. KALTER, and G. W. AJELLO. *Proceedings of the Society for Experimental Biology and Medicine* [*Proc. Soc. exp. Biol.* (*N.Y.*)] **107**, 1–4, May [received July], 1961. 9 refs.

The possible use of fluorescent antibody staining as a simple and rapid method for the identification of polioviruses in stools was investigated by the authors at the Communicable Disease Center, Atlanta, Georgia. The 85 stools examined had previously been tested by routine methods and stored. They were cultivated in monkey kidney tissue culture tubes from which smears were prepared for staining when cytopathic changes reached a 1+ to 2+ reading. Many stools were also tested in tubes containing cover-slips which could be removed for staining. Passage was performed when required and cultures in which cytopathic changes did not appear were stained after 7 days' incubation. Staining was by the direct method, and hyperimmune monkey poliovirus typing sera were used for the preparation of fluorescent antibodies. Particulars are given of the preparation of conjugates and also of the treatment of the stools for inoculation, processing of cultures for staining, conduct of staining, and examination by ultraviolet light microscopy.

The brilliance of the staining and the number of stained cells increased as cytopathic change increased towards the 2+ stage; cultures with a 3+ or 4+ reading did not stain well. Characteristic fluorescent granules were frequently seen in the infected cells in cover-slip preparations, whereas fluorescence in the smear preparations tended to appear as larger cytoplasmic masses. Of 38 polioviruses which had previously been identified, 34 were correctly typed by fluorescent antibody staining. The poliovirus types in the 38 positive stools were: Type 1, 22; Type 2, 2; and Type 3, 14. The failure to detect 4 polioviruses (3 of Type 1 and 1 of Type 3) by fluorescent staining could not be explained, more particularly since cytopathic changes had occurred in their cultures, and 2 of them were successfully typed on re-test by fluorescent staining. The remaining 47 stools were negative for poliovirus both by routine test and by fluorescent staining; this showed that no false positive staining reactions had occurred.

The application of fluorescent antibody staining to the diagnosis of polioviruses is discussed. Although slightly less sensitive than routine procedures, it was entirely specific and future investigation should be directed towards obtaining closer accord between the two methods. Fluorescent staining gave the more rapid results. Hence its utilization as a screening procedure is suggested, in which case routine methods need be applied only to agents failing to give a positive staining reaction. Further, since fluorescent antibody staining demands fewer cultures and fewer manipulations, it effects an economy in time and expenditure which, over a long term, would offset the initial outlay upon equipment.

Joyce Wright

1107. **Studies of Unclassified Mycobacteria. I. *In vivo* Response and Morphologic Studies of a Photochromogen**
D. GALE. *American Review of Respiratory Diseases* [*Amer. Rev. resp. Dis.*] **83**, 718–727, May, 1961. 9 refs.

This paper from the Veterans Administration Hospital, Albuquerque, New Mexico, reports a study of the virulence for mice and guinea-pigs of a photochromogenic acid-fast bacillus isolated from the sputum of a patient with chronic open pulmonary tuberculosis who had been treated with long courses of antituberculous drugs. Groups of 60 mice were given intraperitoneal injections of 700 viable units of the photochromogen together with saline or hog gastric mucin, the organisms and the saline or mucin being injected separately, while 3 groups of 8 guinea-pigs were given approximately 2,000 viable units either intramuscularly or intraperitoneally together with saline or mucin. Animals were killed at regular intervals and the spleen, omentum, lungs, liver, and kidneys examined for the presence of acid-fast bacilli. The findings were compared with those in mice which were given intraperitoneal injections of the H37Rv strain of *Mycobacterium tuberculosis*.

The results indicated that the photochromogen had a greater invasive power than the H37Rv strain. By averaging the number of positive organ cultures an index figure for degree of dissemination was arrived at. For mice injected with mucin this value was 38·3 for the photochromogen and 9·2 for the H37Rv strain. The corresponding figures for mice injected with saline were 23·1 and 1. It was deduced from these and other findings that the photochromogen disseminated more readily and survived better than the H37Rv strain. The effect with 700 viable units of the photochromogen was of the same order as that obtained with 6×10^6 viable units of the H37Rv strain. Histological studies showed proliferation of the photochromogen in the omentum, liver, and lungs of mice receiving the organism plus saline (the controls of the mice receiving the organism plus mucin were unsatisfactory). This showed that the organism had reached the lungs of the mice, although no positive cultures were obtained from the lungs. No lesions were seen in any of the guinea-pigs, regardless of the route of inoculation, except at the site of injection.

Studies of the morphology of the photochromogen showed that the yellow pigmentation was present on the surface of the colony only, that the pigmented organisms had a morphology different from the non-pigmented ones, being longer and wider and containing granules, and that pigmented colonies reverted to the non-pigmented form when reincubated in the dark. Red light was less favourable to pigment formation than light of other wavelengths.

John M. Talbot

1108. **The Arylsulfatase Activity of Acid-fast Bacilli. I. Investigation of Activity of Stock Cultures of Acid-fast Bacilli**

G. P. KUBICA and A. L. VESTAL. *American Review of Respiratory Diseases* [*Amer. Rev. resp. Dis.*] **83**, 728–732, May, 1961. 11 refs.

The arylsulphatase activity of acid-fast bacilli is usually determined by allowing the enzyme to act on tripotassium phenolphthalein disulphate as a substrate and determining the amount of free phenolphthalein liberated by measuring the intensity of the red colour produced after the addition of alkali. In this study reported from the Communicable Disease Center, Atlanta, Georgia, 73 strains of mycobacteria, including 10 strains of *Mycobacterium tuberculosis* and a number of saprophytic and "atypical" strains, were incubated with varying concentrations of substrate for 1 to 3 weeks and the degree of arylsulphatase activity estimated on an arbitrary scale by determining visually the depth of red colour produced by the addition of 2 N sodium hydroxide.

There was a marked lack of arylsulphatase activity in human, bovine, and avian bacilli under these conditions, whereas all the rapidly growing saprophytes, *Myco. fortuitum*, and the unclassified Group-IV "atypical bacilli", as well as the Group-III non-photochromogens, gave positive results. This would appear to be a good method of differentiating Group-III strains from avian strains, which are in other respects very similar. The authors recommend incubation for 2 weeks in 0·0005 M or 0·001 M substrate in "tween"-albumin broth.

John M. Talbot

1109. **The Arylsulfatase Activity of Acid-fast Bacilli. II. The Differentiation of *Mycobacterium avium* from the Unclassified Group III Nonphotochromogenic Mycobacteria**

G. P. KUBICA and R. E. BEAM. *American Review of Respiratory Diseases* [*Amer. Rev. resp. Dis.*] **83**, 733–736, May, 1961. 5 refs.

Using the technique for investigating arylsulphatase activity described in the previous paper [see Abstract 1108], the authors investigated 46 strains of mycobacteria in two groups: (1) 22 known strains of avian mycobacteria and Group-III non-photochromogens (the latter also being known as Battey strains after the place where they were first isolated); and (2) 24 unknown strains which were also typed by animal pathogenicity tests and by growth at various temperatures. Measurement of arylsulphatase activity at the second week proved to be an accurate method of differentiating between avian and Battey strains in both groups. *John M. Talbot*

1110. **The Arylsulfatase Activity of Acid-fast Bacilli. III. Preliminary Investigation of Rapidly Growing Acid-fast Bacilli**

G. P. KUBICA and A. L. RIGDON. *American Review of Respiratory Diseases* [*Amer. Rev. resp. Dis.*] **83**, 737–740, May, 1961. 8 refs.

Twenty-five stock strains of rapidly growing mycobacteria were investigated for arylsulphatase activity by the technique previously described [see Abstract 1108]. They included saprophytes, 9 unclassified Group-IV strains, and 9 strains of *Mycobacterium fortuitum*. In the saprophytes arylsulphatase activity was absent or negligible, whereas it was marked in the strains of *Myco. fortuitum*. The Group-IV strains were intermediate in behaviour. Using this technique in parallel with other definitive biochemical tests, it was possible in most cases correctly to classify 17 unknown freshly isolated strains.

John M. Talbot

1111. **The Specificity of the Passive Hemagglutination Methods used in Serology of Tuberculosis**

Y. TAKAHASHI, S. FUJITA, and A. SASAKI. *Journal of Experimental Medicine* [*J. exp. Med.*] **113**, 1141–1154, June 1, 1961. 30 refs.

The haemagglutination tests used in testing immunity to tuberculosis are of two main types—the Middlebrook–Dubos (M.D.) test using normal erythrocytes and the Boyden test using erythrocytes tanned with tannic acid. It is generally considered that the M.D. test is concerned with polysaccharide antibodies and the Boyden test with antibodies to proteins. It has recently been found by the authors, working at Hokkaido University, Sapporo, Japan, that a phosphatid component of tubercle bacilli is also capable of sensitizing normal sheep erythrocytes to give haemagglutination reactions. Full details of the preparation of the antigens and antisera are given. The results with several antigens showed that if the antigen contained less than 1% of nitrogen it would only sensitize normal erythrocytes—that is, react to the polysaccharide antigen—and likewise that if the protein antigen contained less than 1% of polysaccharide it would not give a positive reaction with the M.D. test. Absorption of the various antisera with erythrocytes to which the different antigens had been bound showed that the respective antibodies for the M.D. test and the Boyden test could be absorbed specifically. It was further shown that the antibodies could be absorbed by using kaolin particles coated with respective antigens and that the phosphatid antibody could also be easily removed from serum by coating kaolin particles with phosphatid antigen. Using these tests it was possible to show that the phosphatid antigen was different from both the polysaccharide and the protein antigens. It was also shown that the polysaccharide antigen does not stick to the surface of tanned erythrocytes and that protein does not stick to normal erythrocytes. These findings seem to remove any doubt as to the specificity of the M.D. and Boyden tests as it is obvious that, in the past, if an impure antiserum was used misleading results would be obtained according to the amount of polysaccharide or protein in the serum. This would also account for discrepancies in the inhibitory test, for in using cross-inhibition tests sensitization of erythrocytes with a polysaccharide antigen would cause some degree of inhibition of the Boyden test if undue amounts of protein antigen were present in the serum.

The authors consider that their findings confirm the value of these serological tests in the study of tuberculosis provided that the antigen and antibodies used are free from undue contamination with non-specific antigenic components. *R. F. Jennison*

Pharmacology and Therapeutics

1112. **Sympathomimetic Drugs in Orthostatic Hypotension**

V. J. PARKS, A. G. SANDISON, S. L. SKINNER, and R. F. WHELAN. *Lancet* [*Lancet*] **1**, 1133–1136, May 27, 1961. 3 figs., 20 refs.

The pressor response to certain sympathomimetic amines such as the amphetamines and ephedrine is often small or absent in patients with autonomic neuropathic orthostatic hypertension. It has been suggested that these compounds act by releasing noradrenaline from stores in the arterial wall. The authors, at the University of Adelaide, therefore observed the responses of the peripheral blood vessels to the direct application of these amines in cases of idiopathic degeneration of the sympathetic nervous system and compared them with the responses of surgically sympathectomized and normal vessels. The responses to noradrenaline and phenylephrine, which act directly on the blood vessels, and to methoxamine and metaraminol, which, it is suggested, act both directly and indirectly, were also observed.

The infusion of 50 μg. of ephedrine or methylamphetamine into the brachial artery during one minute caused a fall in blood flow in the hand in each of 5 normal subjects, and infusion of 500 to 1,000 μg. of either drug in a further 8 normal subjects produced a pronounced fall in blood flow in hand and forearm lasting at least one hour. Doses of 500 μg. in one minute caused no fall in hand blood flow in 2 surgically sympathectomized patients, but 2 others responded normally to ephedrine. The latter 2 patients were considered to be incompletely denervated and were not investigated further. In 2 cases of autonomic degeneration doses of ephedrine or methylamphetamine up to 1,000 μg. per minute for one minute were without effect on hand blood flow. A third patient with autonomic degeneration, who showed incomplete denervation clinically, responded in a normal manner. Infusions of methoxamine, metaraminol, noradrenaline, and phenylephrine produced vasoconstriction in all subjects. *P. A. Nasmyth*

1113. **The Initial Transient Stimulating Action of Neuromuscular Blocking Agents in the Cat**

J. P. PAYNE. *British Journal of Anaesthesia* [*Brit. J. Anaesth.*] 33, 285–288, June, 1961. 1 fig., 8 refs.

The division of relaxants into depolarization and competition blockers is less well defined than had previously been believed and evidence has been presented which, though not conclusive, suggests that all neuromuscular blocking agents pass through a depolarizing phase which is later followed by competition block if the action of the drug is prolonged. The depolarizing phase is extremely short with drugs like tubocurarine and competition block develops early, but with decamethonium and suxamethonium competition block may never be seen unless the block is unduly prolonged.—[Author's summary.]

1114. **Clinical Trial of Librax in Gastrointestinal Disorders**

C. W. HOCK. *Journal of New Drugs* [*J. New Drugs*] **1**, 90–95, March–April [received June], 1961. 16 refs.

The author of this paper from the Medical College of Georgia, Augusta, describes a clinical trial of "librax" (one capsule of which contained 2·5 mg. of clidinium bromide and 5 mg. of chlordiazepoxide) in the treatment of gastro-intestinal disorders associated with symptoms of anxiety and tension. The drug was given to 100 patients (58 male and 42 female, aged 13 to 72 years) in a dosage of one capsule 4 times daily, treatment being continued for 4 to 16 weeks. Each patient was subjected to a complete examination for diagnostic purposes which revealed gastro-intestinal abnormalities in 44, gall-bladder abnormalities in 10, anaemia in 9, abnormal stools in 3, and abnormal urine in 2; in 6, lesions were found on sigmoidoscopy. Most of the patients received additional drugs such as antacids and anti-depressives and all were given some form of anti-ulcer or low-residue diet.

The results were assessed on the basis of improvement in symptoms. They were "excellent" in 20 patients, "good to excellent" in 20, "good" in 36, "fair to good" in 12, "fair" in 9, and "poor" in 3. In some patients who experienced considerable relief of psychic disturbances there was only a "fair to good" response in somatic symptoms. Side-effects included constipation in 21 patients, dryness of the mouth in 4, difficulty in initiating micturition in 3, drowsiness in 2, and headache, decreased libido, blurred vision, epigastric burning, and abdominal pain each in one patient. Side-effects necessitated cessation of therapy in 5 patients.

It is considered that librax is suitable for the treatment of anxious patients with gastro-intestinal disorders and that it minimizes the undesirable side-effects common to anticholinergic agents. *Anne Tothill*

1115. **Diuretic Effectiveness of Trichlormethiazide: a Preliminary Study**

D. O. MINTZ and I. N. ROSENBERG. *Journal of New Drugs* [*J. New Drugs*] **1**, 85–89, March–April [received June], 1961. 2 refs.

A clinical trial of trichlormethiazide, a recently synthesized derivative of chlorothiazide, as a diuretic agent, was carried out on 40 patients at Boston City Hospital, Massachusetts. All the patients had oedema, in 20 from decompensated arteriosclerotic heart disease and in the others from hypertensive heart disease, rheumatic heart disease, cor pulmonale, carcinomatosis, diabetic glomerulosclerosis, or cirrhosis of the liver. They received 10 to 45 mg. of trichlormethiazide daily in divided doses or 10 to 30 mg. daily in single doses. Body weight, blood pressure, and degree of peripheral oedema were recorded 3 to 6 times a week and the serum potas-

sium concentration was determined at the time or within a few days of initiation of trichlormethiazide therapy. Dietary intake of sodium was restricted to 400 to 1,000 mg. daily.

The average weight loss of the entire group over a period of 7 to 9 days was 8·8 lb. (4 kg.), the single-dose schedule being more efficacious than the divided-dose schedule. The drug was most effective in arteriosclerotic heart disease and least effective in patients with cirrhosis. Serial serum potassium levels determined on 31 patients just before or just after administration of trichlormethiazide and within a few days of discontinuing treatment showed that the average initial level was 4·6 mEq. per litre and the final level 4·4 mEq. per litre. Changes in blood pressure were observed in 37 cases. Before treatment the average blood pressure was 133 mm. Hg systolic and 76 mm. Hg diastolic; after treatment for a mean period of 11·8 days (range 5 to 35 days) the average systolic blood pressure was 120 mm. Hg and the diastolic 71 mm. Hg.

The efficacy of trichlormethiazide was compared with that of mercurial compounds in 6 patients and that of chlorothiazide in 3. Mercurial diuretics were more effective in 2 of the 6 patients while chlorothiazide was more effective in all 3 patients given this drug.

Anne Tothill

1116. **Use of Spironolactone in Renal Edema: Effectiveness and Association with Hyperkalemia**

R. T. Manning and F. C. Behrle. *Journal of the American Medical Association* [*J. Amer. med. Ass.*] **176**, 769–771, June 3, 1961. 4 figs., 12 refs.

Excessive excretion of aldosterone has been found to occur in patients with renal oedema which is refractory to the usual treatment with rest in bed, sodium restriction, and administration of corticosteroids and diuretics. The aldosterone antagonist, spironolactone, was tried in the treatment of 6 such patients at the University of Kansas Medical Center, Kansas City. Of the 6 patients, 4 were adults, 3 of whom had renal oedema secondary to diabetes mellitus and one had apparent sulphonamide-induced nephritis. The 2 children had lipoid nephrosis. In 5 of the 6 patients spironolactone in a dosage of 200 to 400 mg. daily was an effective additional form of therapy, with loss of oedema. Hyperkalaemia occurred in 3 patients with severe impairment of renal function, as judged by elevated blood urea nitrogen levels, although one of them had received chlorothiazide concurrently. The authors therefore emphasize that the serum potassium level must be closely observed during spironolactone therapy. Although this drug produced clinical improvement, it did not affect the underlying disease process.

P. T. Main

1117. **Importance of Potassium Supplements during the Use of Spironolactone and Thiazide Diuretics**

E. J. Ross. *British Medical Journal* [*Brit. med. J.*] **1**, 1508–1510, May 27, 1961. 4 figs., 3 refs.

The results of combined therapy with a thiazide diuretic and spironolactone in 4 oedematous patients are described in this paper from University College Hospital Medical School, London. The addition of spironolactone reduced the potassium loss to some extent, but it was found desirable to give a potassium salt by mouth in addition, to avoid potassium depletion. Administration of potassium chloride in a dosage of 6 g. daily in enteric-coated capsules also increased sodium excretion. The author states that in the presence of renal failure potassium salts may cause potassium intoxication and it is therefore necessary to determine the serum potassium level at frequent intervals.

V. J. Woolley

1118. **Spirolactones and Oedema. Further Therapeutic and Biological Studies.** (Spirolactones et oedèmes. Nouvelles études thérapeutiques et biologiques)

P. Vesin, —. Giboudeau, L. Debbasch, —. Etienne, H. Renault, and R. Cattan. *Bulletins et mémoires de la Société médicale des hôpitaux de Paris* [*Bull. Soc. méd. Hôp. Paris*] **77**, 522–531, 1961. 16 refs.

Four cases of oedema are described, one of which ended fatally. They were due to hepatic cirrhosis and had proved resistant to cortisone. Treatment consisted in the administration of a spirolactone, 600 mg. per 24 hours, until a considerable diuresis and loss of weight occurred. It is emphasized, however, that it is important to discontinue treatment with a spirolactone before any sign of dehydration appears, since the diuresis persists for some days after treatment ceases. When the oedema reappears a new course is begun and this alternation can be repeated; 10 mg. of cortisone should also be given daily 5 times a week. Paracentesis should not be attempted and a moderate amount (1 to 1·5 g.) of sodium chloride, can be taken daily. About 20 days' interval can be allowed between treatments, which themselves last 4 to 5 days.

V. J. Woolley

1119. **Clinical Studies of a New Barbiturate (Nealbarbitone)**

A. A. Robin, D. P. Cronin, and L. Scotton. *Journal of Mental Science* [*J. ment. Sci.*] **107**, 83–89, Jan. [received March], 1961. 1 fig., 14 refs.

A comparative study of the therapeutic value of nealbarbitone and amylobarbitone in anxiety states is reported from Runwell and Southend General Hospitals, Essex. Preliminary clinical trials had indicated that nealbarbitone had a sedative action comparable to that of other barbiturates, but did not so easily cause coma with overdosage.

A double-blind cross-over trial was carried out on 20 out-patients who received in random order either nealbarbitone or amylobarbitone for one week in a dosage of 1 gr. (65 mg.) 3 times a day. At the end of the week the alternative drug was given for a similar period. Ratings were made initially and at the end of each week, and at the completion of the fortnight's trial each patient was asked to state the week in which he felt most benefit. Sequential analysis showed that all the patients found amylobarbitone and nealbarbitone equally useful as sedatives; no side-effects were noted with the latter.

A trial of the relative hypnotic activity of the two drugs showed that nealbarbitone has significantly less hypnotic activity than amylobarbitone.

B. M. Davies

Chemotherapy

1120. **A New, Highly Effective but Nontoxic Antibacterial Substance**

D. HALER and A. AEBI. *Nature* [*Nature* (*Lond.*)] **190**, 734–735, May 20, 1961.

A new type of antibacterial substance is reported, which is a polycondensed urea–formaldehyde compound (" anaflex "). It is sparingly soluble in water and shows broad-spectrum bacteriostatic properties when tested by Fleming's ditch and disk methods on solid media and by the addition of a suspension of the compound to liquid media. No resistant organisms have emerged after serial subculturing. The compound has also been used with some success as a topical application for more than 200 patients who were suffering from various superficial infections of bacterial or fungal nature. The mode of action is uncertain; it is probably not due to the liberation of formaldehyde.

[This is an interesting paper, but is very much in the nature of a preliminary note of uncontrolled observations, particularly in regard to the clinical part of the work.]

T. B. Begg

1121. **Uracil Mustard, a New Alkylating Agent for Oral Administration in the Management of Patients with Leukemia and Lymphoma**

B. J. KENNEDY and A. THEOLOGIDES. *New England Journal of Medicine* [*New Engl. J. Med.*] **264**, 790–793, April 20, 1961. 3 figs., 10 refs.

This report on uracil mustard, a new oral alkylating agent in which the methyl group of nitrogen mustard (mustine hydrochloride) is replaced by uracil, in the treatment of leukaemia and lymphoma comes from the University of Minnesota Medical Center. Animal trials have indicated that it is as active as chlorambucil and more effective than nitrogen mustard against a variety of tumours in rodents.

In the therapeutic trial here reported the drug was given by mouth in the form of 1-mg. or 5-mg. capsules. The dosage varied from 5 mg. daily for 2 days to 10 mg. daily for 4 days. When there was complete objective regression the course was not repeated until recurrence of the disease. When there was evidence of improvement the course was repeated at intervals of 2 to 4 weeks until maximum regression was obtained or resistance developed. Some patients have received up to 10 courses in a year. Of the 50 patients treated, 29 had already had various other forms of treatment, mainly radiotherapy. The usual criteria for judging objective response were used, namely, diminution in size of enlarged lymph nodes, spleen, and tumour masses and restoration of blood indices to normal. Subjective improvement was judged by a sense of well-being, increased performance, and relief of pain.

Of 20 patients with chronic lymphatic leukaemia, objective improvement occurred in 15 and subjective improvement in 12. For Hodgkin's disease (14 patients) the corresponding figures were 8 and 8 and for lymphoblastoma (13 patients) 8 and 7. Control of the disease for more than one year was obtained in 7 cases. Subacute lymphatic leukaemia, Kaposi's sarcoma, and mycosis fungoides (one case each) were not improved. Systemic effects were mild. Gastro-intestinal disturbance appeared on the days of administration, while leucopenia and thrombocytopenia occurred between the 7th and 16th days in about one-third of the patients treated, but in no case was there irreversible injury to the haematopoietic tissues.

The results of several other trials are discussed and it is noted that single doses of over 0·2 mg. per kg. body weight have been reported to be myelosuppressive and toxic. The authors conclude that intensive intermittent treatment with short courses is effective and simplifies prolonged therapy for chronic lymphatic leukaemia and malignant lymphoma, but that further investigation is necessary to establish the optimum dosage.

J. S. Malpas

1122. **Treatment of Malignant Disease with an Alkylating Agent: Review of 100 Patients Treated with " Endoxan "**

T. S. REEVE. *Medical Journal of Australia* [*Med. J. Aust.*] **1**, 686–689, May 13, 1961. 5 figs., 7 refs.

At the Royal North Shore Hospital, Sydney, Australia, 100 patients with various forms of malignant disease who were considered unsuitable for surgery or radiotherapy were treated with " endoxan " (cyclophosphamide). The drug was given intravenously in a saline infusion, usually in a single dose of 40 to 100 mg. per kg. body weight (40 to 50 mg. per kg. is considered to be the optimum). An hour before the drug was given each patient received 25 mg. of chlorpromazine and 100 mg. of pentobarbitone intramuscularly. Of the 100 patients, 10 died from the disease within 16 days. There was 80% clinical or radiological regression of tumour for at least 2 months in 12 patients and in 24 there was regression for at least one month. Of the remaining 54, transient regression was observed in 18, an "indeterminate result " in 9, and progression of the tumour in 27. Side-effects included transient leucopenia in all patients after 8 to 12 days and haematuria for 48 hours in 40. Almost complete alopecia of the head and face was seen in 60 cases, with regrowth of hair 3 months later. A table shows that the best results were obtained in cases of cancer of the lung. [None of the patients had Hodgkin's disease and only one had lymphosarcoma.]

The author gives details of 3 cases. It is considered that cyclophosphamide is less toxic than other alkylating agents and that the results justify further trial, even though alopecia is a common side-effect.

K. E. Halnan

Infectious Diseases

1123. **The Treatment of Sarcoidosis with Chloroquine**
S. I. Morse, Z. A. Cohn, J. G. Hirsch, and R. W. Schaedler. *American Journal of Medicine* [*Amer. J. Med.*] **30**, 779–784, May, 1961. 4 figs., 8 refs.

The results of treatment with chloroquine of 7 cases of chronic sarcoidosis are reported from the Rockefeller Institute, New York. There was apparent improvement in the skin lesions in all instances, and the clinical response was associated with a return towards normal of raised erythrocyte sedimentation rates and high gamma-globulin levels. The response in other systems was more variable, but it was most evident when mucosa and thoracic lymph nodes were involved.

D. Geraint James

VIRAL DISEASES

1124. **Recurrent Asian Influenza in an Industrial Population**
N. K. Weaver, J. G. Lione, and W. J. Mogabgab. *Annals of Internal Medicine* [*Ann. intern. Med.*] **54**, 843–855, May, 1961. 3 figs., 17 refs.

An investigation is reported of two outbreaks of influenza due to virus A2 in an industrial population which had been offered influenza immunization annually since 1957. The subjects were employees of a large petroleum refinery and petrochemical plant in Baton Rouge, Louisiana. The illness began suddenly in September, 1957, and continued into the spring of 1958, the monthly attack rates showing peaks of 34 cases per 1,000 employees in October, 1957, and 47 per 1,000 in February, 1958, the over-all rate for the period September, 1957, to March, 1958, inclusive, being 186 per 1,000. A few cases of Asian influenza occurred among the employees between September, 1958, and March, 1959, but none in the autumn of the latter year. However, in the middle of January, 1960, there was a sharp, explosive outbreak which continued for about 8 weeks, with a peak monthly attack rate of 78 per 1,000 employees in February and an over-all attack rate of 109 per 1,000 for the season. Absentee rates among the employees for all respiratory diseases followed closely the monthly attack rates for influenza—210 days' absence per 1,000 workers in October, 1957, 300 per 1,000 in February, 1958, and 500 per 1,000 in February, 1960, corresponding to the peaks in incidence of influenza.

The results of laboratory studies provided aetiological confirmation of the respiratory illness, antigenically identical strains of Asian influenza virus being isolated in both epidemics. Clinical and epidemiological observations of the appearance and re-appearance of Asian influenza in the population were also corroborated by isolation of the virus and the results of serological studies during the 3-year period. Vaccination gave significant protection to inoculated workers during the epidemics. It was offered to the employees each autumn and winter during the 3-year period, but observations suggested that immunity may have been declining 4 months after vaccination, this view being supported by the fact that there was no evidence of vaccine protection being carried over from one year to the next. The authors consider it possible that two 0·5-ml. doses (250 chick-cell agglutination units each) spaced more widely apart (September and December) might afford equal or better protection, with fewer reactions, than the scheme of vaccination conventionally recommended. Although this would not evoke as great an antibody response as a larger total dose, it would result in the peak titres occurring at a time when they were most needed.

R. G. Meyer

1125. **Respiratory Syncytial Virus. I. Virus Recovery and Other Observations during 1960 Outbreak of Bronchiolitis, Pneumonia, and Minor Respiratory Diseases in Children**
R. M. Chanock, Hyun Wha Kim, A. J. Vargosko, A. Deleva, K. M. Johnson, C. Cumming, and R. H. Parrott. *Journal of the American Medical Association* [*J. Amer. med. Ass.*] **176**, 647–653, May 27, 1961. 7 refs.

Since the isolation, in 1956, of a new virus from a chimpanzee with coryza evidence has been sought concerning its pathogenicity for the human respiratory tract. This paper from the National Institutes of Health and the Children's Hospital of the District of Columbia, Washington, reports an investigation of the incidence of this virus, known as respiratory syncytial (R.S.) virus, among 346 infants and young children with acute lower respiratory-tract disease and 272 controls admitted to hospital between March and July, 1960. Virus isolation was undertaken by inoculation of unfrozen throat-swab specimens directly into tissue cultures of a human epithelial cell line (HEp-2) maintained in Eagle's medium with 5% added chicken serum. The cytopathic effect of the virus was shown by the formation of syncytia and was usually evident 6 to 14 days after inoculation, but occasionally not until the 22nd day. Identification was completed by complement fixation using a hyperimmune guinea-pig serum. In a proportion of the children the serological response to infection was studied by neutralization and complement fixation tests.

R.S. virus was isolated from 56 children with respiratory disease and from 4 controls. The highest isolation rate occurred in infants under 7 months with bronchiolitis; in these it was 59%. Seven of 13 infants under 7 months with pneumonia also yielded the virus, whereas the isolation rate in infants with minor respiratory disease was 19% and in those without respiratory illness no virus was found. The complement fixation test with the antigens available was found to be relatively insensitive as an indicator of infection and in the neutralization test the interpretation was beset with the added complica-

tion of a possible non-specific inhibitor in the patients' sera.

(In an addendum the authors mention a further period of prevalence of infection by R.S. virus in the winter of 1960–1 in which they recovered virus from 93 of 521 individuals with respiratory disease and from one of 227 control subjects. Again virus was isolated most frequently from infants suffering from bronchiolitis and pneumonia.) *J. E. M. Whitehead*

1126. **Respiratory Syncytial Virus. II. Serologic Studies over a 34-month Period of Children with Bronchiolitis, Pneumonia, and Minor Respiratory Diseases**
R. H. PARROTT, A. J. VARGOSKO, HYUN WHA KIM, C. CUMMING, H. TURNER, R. J. HUEBNER, and R. M. CHANOCK. *Journal of the American Medical Association* [*J. Amer. med. Ass.*] **176**, 653–657, May 27, 1961. 1 fig., 9 refs.

Evidence of infection by respiratory syncytial (R.S.) virus [see Abstract 1125] was sought by serological methods in infants and children admitted to the Children's Hospital of the District of Columbia, Washington, from October, 1957, to July, 1960, with acute respiratory illness. Sera were examined by the complement fixation test, but the significance of a rise in antibody titre shown in this way could not properly be assessed until a change in technique enabled the R.S. virus to be isolated with greater frequency from such patients. The technical procedure leading to this was the inoculation of throat-swab fluids without prior freezing directly into tissue cultures. The increased rate of isolation thus obtained in the later stages of the investigation enabled the serological data obtained earlier to be reinterpreted.

It was estimated that evidence of infection was present in 21% of 1,038 infants and children admitted with a diagnosis of pneumonia, bronchiolitis, croup, or pharyngitis with bronchitis. This was 5·5 times greater than the rate observed in control subjects without respiratory disease. The greatest association of infection by R.S. virus was found among infants rather than older children and among cases of bronchiolitis and bronchopneumonia. During the period of the survey there were 3 periods when evidence of infection was prevalent as judged by the results of serological examinations, and these coincided with the peaks of prevalence of respiratory illness. *J. E. M. Whitehead*

1127. **Respiratory Syncytial Virus. III. Production of Illness and Clinical Observations in Adult Volunteers**
H. M. KRAVETZ, V. KNIGHT, R. M. CHANOCK, J. A. MORRIS, K. M. JOHNSON, D. RIFKIND, and J. P. UTZ. *Journal of the American Medical Association* [*J. Amer. med. Ass.*] **176**, 657–663, May 27, 1961. 2 figs., 12 refs.

Adult volunteers from a federal "correctional institution" were inoculated with second monkey kidney passage R.S. virus by spraying approximately 1 ml. of virus inoculum into the nose and throat followed by instillation of 0·5 ml. into each nostril while the subject was supine. The virus was administered to 41 volunteers in doses of 160 to 640 tissue-culture doses, and after an incubation period of nearly 5 days 20 of those inoculated developed symptoms of a common cold lasting 5 to 6 days. The symptoms were milder than those produced by natural infection by R.S. virus in children and this was attributed to previous exposure to the virus as evidenced by the finding of neutralizing antibody in the pre-inoculation sera. Virus was isolated from 85% of those inoculated who developed symptoms and from 62% of those who did not. Some of the material inoculated was found to be contaminated by a latent monkey virus, SV 40, and this induced a fourfold rise in antibody titre in 21 of 33 persons to whom it was accidentally given, but it failed to produce symptoms.
J. E. M. Whitehead

1128. **Respiratory Syncytial Virus. IV. Correlation of Virus Shedding, Serologic Response, and Illness in Adult Volunteers**
K. M. JOHNSON, R. M. CHANOCK, D. RIFKIND, H. M. KRAVETZ, and V. KNIGHT. *Journal of the American Medical Association* [*J. Amer. med. Ass.*] **167**, 663–667, May 27, 1961. 1 fig., 6 refs.

This paper supplements the clinical observations, reported in the previous paper [see Abstract 1127], made on 41 volunteers inoculated with respiratory syncytial (R.S.) virus. The results of virus isolation from throat swabs, which were considered superior to nasal swabs for this purpose, showed that recovery of virus coincided with the development of symptoms and was also detectable for longer periods in those subjects who developed symptoms than in those who did not, thus strengthening the causal association between R.S. virus and the respiratory symptoms. Antibody response was also more obvious in those volunteers who developed symptoms. Although all the inoculated individuals had pre-existing antibody in the serum, no correlation between its titre and the development of symptoms was observed. Of the 41 persons inoculated, 33 showed laboratory evidence of infection and 21 developed the symptoms of a cold.
J. E. M. Whitehead

1129. **Studies of Acute Respiratory Illnesses Caused by Respiratory Syncytial Virus. 2. Epidemiology and Assessment of Importance**
L. MCCLELLAND, M. R. HILLEMAN, V. V. HAMPARIAN, A. KETLER, C. M. REILLY, D. CORNFELD, and J. STOKES JR. *New England Journal of Medicine* [*New Engl. J. Med.*] **264**, 1169–1175, June 8, 1961. 6 refs.

Evidence of the important aetiological role of respiratory syncytial (R.S.) virus in acute respiratory-tract illness in children is presented in this paper. The analysis is based upon epidemiological and clinical investigations made at the Hospital of the University of Pennsylvania and the Children's Hospital of Philadelphia between October, 1959, and June, 1960. Diagnosis of R.S. virus infection depended mainly upon serological tests, as described in Part 3 [see Abstract 1130]. (Particulars of the laboratory investigations (Part 1 of this study) will be published later.)

Among 563 children attending or admitted to the 2 hospitals with acute respiratory-tract illness, R.S. virus infection was diagnosed in 109 (19%); it accounted for 59 (14%) of 408 illnesses of the upper respiratory tract,

1 (9%) of 11 cases of croup, and 49 (34%) of 144 illnesses of the lower respiratory tract. Thus R.S. virus infection was proportionally of greater importance in lower than in upper respiratory-tract illness and occurred in 22 (39%) of 56 cases of bronchopneumonia, 10 (38%) of 26 cases of bronchiolitis, and 17 (27%) of 62 cases of bronchitis. In contrast, R.S. virus infection occurred in only 3 (2·7%) of 113 children without respiratory-tract disease. R.S. virus infections occurred principally as an epidemic in March, April, and May, 1960, during which time 103 of the 109 cases were observed. The virus accounted for 50% of the cases of lower and for 29% of those of upper respiratory-tract illness observed during this 3-month period. The 563 children ranged in age from 1 month to 10 years, with the greater number aged 2 years or less. Both upper and lower respiratory-tract illnesses due to R.S. virus occurred among children in all age groups. The incidence of R.S. virus infection by year of age was remarkably constant (20 to 22%) within the age range 1 month to 4 years. With increase in age there was a decline in incidence, which was 18% at 5 years, 13% at 6 years, and 5% at 7 years; this suggested that most children develop immunity to R.S. virus by early school age.

Serological evidence also indicated that experience of R.S. virus is gained in childhood. Thus among 541 children with illnesses not caused by R.S. virus complement fixation tests on single serum samples showed an incidence of 63 to 68% of positive reactors to R.S. virus in the age range 5 to 10 years; this was comparable with the adult incidence of 67%. Among younger children the incidence of positive reactors rose with increasing age from 6% at 6 to 11 months to 56% at 4 years. Maternal antibody was present in some of the very young infants.

During an earlier period (January to September, 1959), when investigations were being undertaken in only one of the two hospitals, R.S. virus infection occurred in 6 of 104 children with respiratory-tract infection and in none of 40 children in a control group. *Joyce Wright*

1130. **Studies of Acute Respiratory Illnesses Caused by Respiratory Syncytial Virus. 3. Clinical and Laboratory Findings**

C. M. Reilly, J. Stokes Jr., L. McClelland, D. Cornfeld, V. V. Hamparian, A. Ketler, and M. R. Hilleman. *New England Journal of Medicine* [*New Engl. J. Med.*] **264**, 1176–1182, June 8, 1961. 1 fig., 9 refs.

This paper records the clinical and laboratory findings in 109 children with acute respiratory tract illness due to respiratory syncytial (R.S.) virus [see Abstract 1129]. Diagnosis depended mainly upon a fourfold or greater increase in complement-fixing antibody against R.S. virus during convalescence. Confirmatory serum neutralization reactions were obtained in 33 of 34 patients. The virus was isolated from the respiratory-tract secretions of 21 of 34 patients, whereas bacteriological examination of these specimens yielded no evidence of primary bacterial causation. Serum samples from the 109 patients and from 113 control patients were also tested against influenza (A_1, A_2, B, C), Coxsackie, Coe, and Pett viruses, *Myxovirus parainfluenzae* (1, 2, 3), adenovirus, and reovirus group, but with negative results.

Most of the children were treated in the out-patient clinics where, at their first attendance, they were given "a complete hospital-admission type of physical examination". The percentage incidence of 14 signs and symptoms found at the first visit are related, in a figure, to the four main clinical categories of the final diagnosis, namely, upper respiratory-tract illness, bronchopneumonia, bronchiolitis, and bronchitis. Four representative case-reports are given. Among the 109 patients with R.S. virus infection, upper respiratory-tract illnesses occurred in 59 (54%) and lower respiratory-tract illnesses in 49 (45%). There was also one case of croup. The most common clinical features were rhinitis (62 cases), non-productive cough (104) which was often persistent, and fever (100). Pharyngitis (51 cases) occurred, but without exudate, sore throat, or dysphagia. Cervical adenitis (24 cases), catarrhal otitis media (18), mild catarrhal conjunctivitis (14), and vomiting (32) were also noted. The pulse rate was commensurate with fever. The respiration rate was significantly increased in the presence of bronchopneumonia, bronchiolitis, and bronchitis. Detailed clinical descriptions of these three conditions are given. Antibiotic therapy or chemotherapy was employed in 67 cases (61%), but did not generally produce rapid clinical improvement.

The clinical features of R.S. virus infection are compared with those of other respiratory-tract illnesses, namely, adenovirus infection, influenza, common cold, and streptococcal sore throat. The recent description of hitherto unknown viruses is allowing physicians, virologists, and epidemiologists, in coordinated investigations, to seek and find distinguishable syndromes among the acute respiratory-tract illnesses of childhood. The present report describes one part only of a large collaborative research undertaken in Philadelphia.

Joyce Wright

1131. **Epidemic Pleurodynia (Bornholm Disease) Due to Coxsackie B-5 Virus. The Interrelationship of Pleurodynia, Benign Pericarditis, and Aseptic Meningitis**

H. W. Bain, D. M. McLean, and S. J. Walker. *Pediatrics* [*Pediatrics*] **27**, 889–903, June, 1961. 38 refs.

This report deals with 69 children admitted to the Hospital for Sick Children, Toronto, with epidemic pleurodynia (36), acute benign pericarditis (7), and aseptic meningitis (26) between July and October, 1958, during a widespread outbreak of Coxsackie B5 virus infection.

The majority of the 36 cases of epidemic pleurodynia were seen during the months of August and September. Most of the patients were between 4 and 14 years of age; there were also 2 young infants. The duration of the illness averaged 7 days and there were no complications in this particular series (one doctor with pleurodynia developed orchitis). The chief clinical feature was pain in the upper abdomen or lower chest; it had a sudden onset and then acute exacerbations occurred spasmodically. A pleural friction rub was present in 7 children. Fever was variable, and vomiting occurred in 7 cases; the children did not appear ill. Virus studies were

carried out in 21 cases; in 19 of these Coxsackie B5 virus was isolated from the stools (6 of these had an associated aseptic meningitis). A rising titre against Coxsackie B5 virus was noted in 12 out of 15 cases tested.

Of the 7 children with acute benign pericarditis, 5 had pleurodynia as well. A pericardial rub was detected in all 7 cases and persisted up to 2 weeks; in 4 of the 5 with pleurodynia both pericardial and pleural rubs were heard. Pain was a feature only when pleurodynia was present. The heart was enlarged in 5 and there were non-specific changes in the T wave. All recovered rapidly, but a report is given of a boy in a previous epidemic who subsequently developed constrictive pericarditis. Coxsackie B5 virus was isolated from the stools of 5 children, and a rising serum titre was noted in all 7 cases.

Altogether 69 cases of aseptic meningitis are mentioned as occurring between June and December, 1958. Coxsackie B5 virus was isolated from the cerebrospinal fluid in 17 out of 46 tested and from the stools in 33 out of 43 tested. Seven of these patients in whom the aseptic meningitis was associated with pleurodynia are included among the 36 patients with the latter disease.

It is concluded that Coxsackie B5 virus was the common infecting agent in the three syndromes encountered in this outbreak; also that " it seems likely that the Coxsackie B viruses may be important etiologic agents in acute benign pericarditis ". *John Fry*

1132. **Studies with Live Attenuated Measles-virus Vaccine. I. Clinical and Immunologic Responses in Institutionalized Children**

F. R. McCrumb Jr., S. Kress, E. Saunders, M. J. Snyder, and A. E. Schluederberg. *American Journal of Diseases of Children* [*Amer. J. Dis. Child.*] **101**, 689–700, June, 1961. 6 figs., 27 refs.

A 2-year study of 5 lots of live attenuated measles virus vaccine (Edmonston strain, adapted to canine renal cells) on institutionalized children in an attempt to evaluate reactivity and immunogenicity is reported from the University of Maryland School of Medicine, Baltimore. The vaccine was administered to 81 susceptible children intramuscularly (49), intranasally (19), as an aerosol (11), and into the lower conjunctival sac (2), and 71 of the children were successfully immunized. Five to 16 days after immunization nearly all had a mild febrile reaction lasting up to 6 days (mean 3 days), often with a macular rash on or about the 4th day and lasting one to 7 (mean 3·6) days. Respiratory symptoms occurred in less than half and were mild. The respiratory route appeared to be the most innocuous and the intranasal, which was the route of administration in all 10 cases of failure, the least successful. The attenuated virus was isolated from 3 out of 39 specimens of blood or oro-pharyngeal secretions collected from 13 immunized children on the 1st to 4th days of infection, but no evidence of transmission to non-immune contacts were detected.

Good neutralizing and complement-fixing antibody response was obtained, the former being well maintained for at least 16 months, the latter declining after 6 weeks. Vaccination or revaccination of 19 children with pre-existing antibody resulted in no reaction or serological response. On exposure to measles 10 to 15 months after immunization there were no cases of the disease in vaccinated subjects.

[Many problems still remain, especially that of the accompanying modified disease, which must be prevented or at least minimized, before this vaccine can be considered for large-scale use.] *Kurt Schwarz*

1133. **Studies with Live Attenuated Measles-virus Vaccine. II. Clinical and Immunologic Response of Children in an Open Community**

S. Kress, A. E. Schluederberg, R. B. Hornick, L. J. Morse, J. L. Cole, E. A. Slater, and F. R. McCrumb Jr. *American Journal of Diseases of Children* [*Amer. J. Dis. Child.*] **101**, 701–707, June, 1961. 4 refs.

Further observations on immunization with live attenuated measles virus vaccine [see Abstract 1132] were carried out in an open (school) community using 4 lots of vaccine prepared in canine renal cell cultures given via the respiratory route (intranasally and as an aerosol) and a single lot of vaccine prepared from chick embryo cell culture and given by intramuscular injection. It was found that the latter compared fairly well with the other cultures, but had the same disadvantages. An immune response to aerosol vaccination was obtained in 28 out of 30 children, to intranasal vaccination in 42 out of 102 children, and to intramuscular vaccination in 39 out of 41 children.

Encouraging results were obtained with pooled human γ globulin with a neutralizing antibody titre of 1:1,280 administered by intramuscular injection 7 days after intramuscular immunization, the intensity of the reaction being reduced without apparent interference with immunogenicity. All of 12 children immunized in this way developed an immune reaction. *Kurt Schwarz*

1134. **Studies with Live Attenuated Measles-virus Vaccine. III. Development of a Practical Method for Large-scale Immunization**

F. R. McCrumb Jr., R. B. Hornick, S. Kress, A. E. Schluederberg, M. J. Snyder, S. Musser, and T. Bigbee. *American Journal of Diseases of Children* [*Amer. J. Dis. Child.*] **101**, 708–712, June, 1961. 1 fig., 11 refs.

On the basis of their previous experience [see Abstract 1133] the authors successfully immunized 143 (91%) of 158 susceptible school-children by means of an infection induced with live attenuated measles virus vaccine modified by the administration of pooled human γ globulin. One ml. of culture was given by intramuscular injection, followed 3 to 5 days later by 0·02 ml. per lb. (0·044 ml. per kg.) body weight of a γ-globulin preparation with a neutralizing antibody titre of 1:1,280. Reactions were appreciably reduced in frequency, but still occurred (fever in 9 to 13% and rash in 4 to 17% of children). Neutralizing and complement-fixing antibody titres were found to be satisfactory after 44 days.

[These results bring immunization against measles within the realm of practicability, and the results of field trials should show the value of this combined method.] *Kurt Schwarz*

Tuberculosis

1135. **Freeze-dried B.C.G. Vaccine from an Isoniazid-resistant Strain: a Laboratory Investigation**
J. UNGAR, V. THOMAS, and P. W. MUGGLETON. *British Medical Journal* [*Brit. med. J.*] **1**, 1498–1500, May 27, 1961. 9 refs.

B.C.G. vaccine prepared from isoniazid-resistant strains has potential advantages for use in contacts receiving prophylactic treatment with isoniazid; the preparation and laboratory testing of resistant B.C.G. is described in this paper. Cultures of the Copenhagen sub-strain (1954) were incubated with decreasing concentrations of isoniazid (double dilutions of 100 μg. per ml., 50 μg. per ml., 25 μg. per ml., etc.). The culture containing the highest concentration of isoniazid showing visible growth was used as an inoculum for a further growth. This process was repeated until 14 transfers had been made. Resistance to isoniazid at 25 μg. per ml. gradually developed; when this level was reached further transfers failed to increase the resistance. Freeze-dried master cultures of the resistant sub-strain were prepared. These sub-strains grew poorly on Dubos's medium—this phenomenon was associated with an inability to produce catalase—but grew freely on some other media. Morphologically, the resistant and sensitive cultures were identical, and the avirulent character of the originally sensitive strain was maintained in the "trained" resistant sub-strain. Guinea-pigs treated orally with isoniazid became tuberculin-positive when vaccinated with small doses of the resistant sub-strain. In contrast, when a control isoniazid-sensitive B.C.G. sub-strain was used tuberculin conversion was inhibited by isoniazid. *T. M. Pollock*

1136. **A Freeze-dried Vaccine from Isoniazid-resistant B.C.G.: a Clinical Investigation**
W. GAISFORD and M. I. GRIFFITHS. *British Medical Journal* [*Brit. med. J.*] **1**, 1500–1501, May 27, 1961. 3 refs.

An investigation was undertaken in the Department of Child Health, University of Manchester, to assess the degree of cutaneous tuberculin sensitivity after: (1) vaccination with isoniazid-resistant B.C.G. in 60 infants receiving isoniazid by mouth in a dose of 10 mg. per lb. (22 mg. per kg.) per day; (2) vaccination with isoniazid-sensitive B.C.G. of 25 infants receiving isoniazid in the same dosage; and (3) vaccination of a total of 306 untreated infants with an equal dose of either resistant B.C.G. or sensitive B.C.G. A fourth study was made of the persistence of sensitivity up to 2 years after vaccination with both types of vaccine.

In isoniazid-treated infants the resistant vaccine produced satisfactory tuberculin conversion, whereas conversion after the sensitive vaccine was seriously impaired. In untreated infants the resistant vaccine was slightly more antigenic than the sensitive vaccine. The resistant vaccine caused no complications; the tuberculin sensitivity 2 years after vaccination with this was as satisfactory as after the use of the sensitive vaccine. It is concluded that in appropriate circumstances B.C.G. vaccine prepared from isoniazid-resistant strains may be recommended. *T. M. Pollock*

1137. **Tuberculosis Trends in Hong Kong—a Major Victory for B.C.G. Vaccination?**
A. S. MOODIE. *Indian Journal of Tuberculosis* [*Indian J. Tuberc.*] **8**, 59–67, March [received June], 1961. 12 figs.

The author of this paper from Wanchai Chest Clinic, Hong Kong, first points out that this is not a controlled study, but rather an "evaluation of a practical programme developed with a minimum of resources to meet a tuberculosis situation of almost epidemic proportions under the most trying economic and environmental circumstances". In the 400 square miles of Hong Kong the growth of population has been rapid and recent and in many parts there is a complete absence of even the most primitive sanitary facilities. The bulk of the population is still accommodated in the traditional type of overcrowded tenement.

In 1951 one death in every 5 was due to tuberculosis, almost 40% of the deaths occurring in children under 5 years of age. At the same time 2% of the adult population had active tuberculosis. To deal with this problem there were two large out-patient clinics and about 500 hospital beds. It was decided to centre the control programme on the clinics, to use the hospital for cases in which there was a definite prospect of recovery, and to give B.C.G. vaccination on the widest scale, the help of the World Health Organization (W.H.O.) being enlisted for the B.C.G. campaign. Preliminary investigation showed that 36% of subjects under 6 years of age and 77% of those aged 7 to 14 years gave a positive reaction to the Mantoux test—a blacker picture than that seen in any other part of the world. In the special circumstances it was decided, contrary to the usual W.H.O. policy, to give vaccination at birth, 20 mg. of vaccine being given by multipuncture. Conversion rates between 60% and 90% were obtained. In 1960 some 71% of newborn infants were so vaccinated. Simultaneously chemotherapy was greatly extended, approximately 25,000 patients receiving chemotherapeutic drugs in 1960. By 1959 the average age at death from tuberculosis had been raised from 25 to 37 years; further, tuberculosis as a cause of death had fallen from first to third place—10·8% of all deaths as against 20·4% in 1951 and 20% in children under 5 years of age as against 40%.

Thus, the author states, the whole picture has changed and tuberculosis is becoming more a disease of the older age groups. There appears to have been some factor which has reduced the infant mortality rate from tuber-

culosis twice as rapidly as the rate from all causes, and he considers that B.C.G. vaccination is the only factor which could produce such a selective effect on morbidity.

Norman F. Smith

1138. **Antituberculous Vaccination of Infected Adults.** (К противотуберкулезной вакцинации инфицированных взрослых)
G. G. KARAPETJAN. *Проблемы Туберкулеза* [*Probl. Tuberk.*] **39**, 8–15, No. 3, 1961.

The fact that over 90% of cases of active tuberculosis in adults occur as a secondary reinfection makes necessary the development of further prophylactic methods. A pilot scheme was started in February, 1955, when 376 students with a positive Pirquet reaction and no evidence of active disease were vaccinated with B.C.G. without adverse results. Since then a mass vaccination of the population has been carried out. This included all who had a positive Pirquet reaction as read at 48 to 72 hours and whose chest radiograph showed no evidence of active disease. In some areas where x-ray facilities were not available the vaccine was given only if the papule of the Pirquet reaction was less than 10 mm. in diameter. Evidence of old lesions was not considered a contraindication. Children and adolescents were vaccinated whether the Pirquet reaction was positive or negative. Every 1½ to 2 months the subjects were examined with special reference to the peripheral lymph nodes. It was the practice to repeat the Pirquet test every 6 months.

Altogether, 6,274 subjects aged 18 to 50 were given the vaccine by the intradermal route, the control group consisting of 6,000 closely comparable subjects. The reaction in the peripheral lymph nodes was relatively strong and lasted up to 8 or 9 months. Not a single case of suppuration was observed. Local reaction was mild and only occasionally lupus-like changes (0·15%) and Koch's phenomenon (0·3%) were observed. A further 3,564 subjects aged 18 to 50 were given the vaccine by mouth (de Assis's method). Only a few took 6 doses (100 mg. each), the majority refusing to take any more after the 3rd to 5th dose. No gastro-intestinal disturbances were noted. The mesenteric lymph nodes were palpable for 3 to 4 months in a few cases and for 4 to 6 months only in occasional cases. The efficacy of the vaccination of persons with a positive Pirquet reaction could be expressed as follows. If the incidence of the disease in the control group is taken as $100 \pm 26{\cdot}3$ the figures for the groups vaccinated intradermally and by mouth are respectively $23{\cdot}6 \pm 14{\cdot}0$ and $36{\cdot}8 \pm 21{\cdot}0$. The intradermal method has proved more efficacious and also more acceptable and more economical than oral vaccination. Development of an immunoanergic state has not been observed in patients vaccinated by de Assis's method. Changes in the allergic reaction as observed in the two groups of patients are discussed.

S. W. Waydenfeld

1139. **Sputum Induction with Heated Aerosol Inhalations for the Diagnosis of Tuberculosis**
J. P. LILLEHEI. *American Review of Respiratory Diseases* [*Amer. Rev. resp. Dis.*] **84**, 276–278, Aug., 1961. 2 figs., 13 refs.

1140. **A Trial of Double-dose B.C.G. Vaccination of the Newborn (Preliminary Report).** (Из опыта применения удвоенных доз вакцины БЦЖ у новорожденных (Предварительное сообщение))
A. S. NAMOLAT, M. S. DVOJRIN, L. JA. ZAMDBORG, N. F. KOVOROTNAJA, and R. I. ÈJDEL'MAN. *Проблемы Туберкулеза* [*Probl. Tuberk.*] **39**, 16–22, No. 3, 1961. 6 refs.

Calmette's original method of administration of B.C.G. vaccine by mouth has been displaced by the intradermal method. However, it was found that the incidence of tuberculous meningitis was lower among children 2 to 14 years old vaccinated by Calmette's method than among those under 2 who were vaccinated intradermally. The latter method also gives rise to complications not associated with the former, though in the usual dosage the oral method is less effective.

All newborn infants in the town of Cherigor were given 3 double doses (20 mg.) of B.C.G. vaccine orally, while in the town of Nezhin the usual dosage (10 mg. × 3) was continued. In the former group post-vaccination allergy as indicated by the Mantoux reaction (1:100) appeared as early as 3 months (43%) and reached 67% in 6 months. If an area of infiltration of less than 0·5 mm. in diameter were included the latter figure became 89%. In the control group the figure at 3 months was 2% and at 6 months 8%, these figures not being substantially increased by including the weaker reactions. All possible other factors (such as type of feeding, general care, and use of different batches of vaccine) were excluded. It is suggested that an isolation period of 1½ months after B.C.G. vaccination is insufficient and should be extended.

S. W. Waydenfeld

1141. **Results of Subcostal Plombage in Pulmonary Tuberculosis with a Consideration of Changing Indications**
A. A. LEFEMINE, W. W. WILSON, and D. E. HARKEN. *Journal of Thoracic and Cardiovascular Surgery* [*J. thorac. cardiovasc. Surg.*] **41**, 561–571, May, 1961. 7 figs., 5 refs.

Between 1952 and 1956 inclusive, subcostal extraperiosteal plombage was performed 98 times on 90 patients at the Rutland Heights Veterans Administration Hospital, Rutland, Massachusetts (8 patients underwent bilateral operations). Plombage was restricted to those patients in whom resection was not considered advisable because of active disease, drug resistance, poor pulmonary function, extensive bilateral disease, or complicating medical conditions. In most cases the indication for plombage was cavitary disease in the upper lobes, usually with a positive sputum, persisting in spite of adequate medical treatment. Large peripheral thin-walled cavities were regarded as a contraindication because of the risk of erosion.

The standard technique employed consisted in a tailored extraperiosteal dissection from the second to the 6th or 7th rib (one or two ribs below the limit of the disease which it was desired to collapse), freeing the apex from the outer margin of the first rib (but no stripping on the mediastinal aspect), and insertion of polyethylene spheres into the subcostal space. The spheres were strung together in groups of 10 to prevent migration, and

enough were used to provide firm but not excessive compression of the lung.

There were 2 deaths in the immediate postoperative period—one from respiratory insufficiency and one from infective hepatitis—and 4 late deaths—one from a bleeding ulcer, one from cor pulmonale, one after a second-stage thoracoplasty for sepsis, and one after resection. In 9 cases (including 2 of the fatal ones) sepsis, which was usually due to *Staphylococcus aureus*, necessitated removal of the spheres and conversion to standard thoracoplasty; 2 of these patients had bronchopleural fistulae. Sputum conversion was the only criterion of success as it was found impossible radiologically to assess the efficacy of the collapse. At 8 months after operation only 30 of the 74 sputum-positive patients had converted, but as a result of chemotherapy or resection at a later date 56 patients were eventually sputum-negative. Resection was undertaken on 22 patients in whom plombage was unsuccessful, usually within a year; one patient died, in one resection was a failure, and in 2 bronchopleural fistulae developed which required further surgery. *F. J. Sambrook Gowar*

1142. **The Diffuse Obstructive Pulmonary Syndrome in a Tuberculosis Sanatorium. I. Etiologic Factors**
W. Y. Hallett and C. J. Martin. *Annals of Internal Medicine* [*Ann. intern. Med.*] **54**, 1146–1155, June, 1961. 3 figs., 28 refs.

The maximum expiratory flow rate and vital capacity were measured in 710 tuberculous patients admitted to Firland Sanatorium, Seattle, Washington, during the year ending October, 1959. These values, together with data on the extent of the tuberculous disease, were recorded on cards and analysed. The diffuse pulmonary obstructive syndrome was found in 241 (34%) of the patients and the analysis showed that the patient's age and extent of the tuberculous disease were statistically significant factors in aetiology. A significantly high incidence was also found in patients with asthma (but not other allergic conditions), pulmonary malignant disease, silicosis, and a history of frequent protracted chest colds. Over 100 other diseases present at the time of admission and also the patients' smoking habits were examined to detect any possible relationship between them and the syndrome, but when allowance was made for the patient's age in each case the results were negative. *B. Golberg*

1143. **The Diffuse Obstructive Pulmonary Syndrome in a Tuberculosis Sanatorium. II. Incidence and Symptoms**
C. J. Martin and W. Y. Hallett. *Annals of Internal Medicine* [*Ann. intern. Med.*] **54**, 1156–1164, June, 1961. 2 figs., 19 refs.

In all cases found in the authors' study described above [see Abstract 1142] in which the patient's maximum expiratory flow rate or vital capacity was abnormal further studies of cardiopulmonary function were carried out these including determination of maximum breathing capacity, with and without the use of bronchodilator drugs, and the degree of oxygen saturation, CO_2 content, and *p*H of the blood.

Of the 241 patients (34%) with maximum expiratory flow rates (M.E.F.) below normal (that is, 260 litres per minute for men and 210 litres per minute for women) mild obstructive airway disease (M.E.F. not less than 160 litres per minute) was present in 111 (15%), but these patients were mostly asymptomatic. Moderate obstruction (M.E.F. 110 to 160 litres per minute) was present in 76 patients (11%) and severe obstruction (M.E.F. below 110 litres per minute) in 54. The maximum breathing capacity (M.B.C.) correlated well with the M.E.F. in 168 patients with a low M.E.F. In 70% of 102 patients the rise in the predicted M.B.C. after inhalation of a bronchodilator aerosol was less than 12% and was unrelated to the severity of the airway obstruction. The vital capacity was significantly related to the M.E.F. Blood gas analysis in patients with an M.E.F. of less than 110 litres per minute revealed an arterial blood oxygen saturation of 94% or less in 31 patients (4%), while in 8 male patients the pCO_2 was greater than 4 mm. Hg. The degree of dyspnoea and the severity of cough correlated well with the presence of airway obstruction, and abnormal flow rates were also usually present in those with purulent or profuse sputum. Radiographic findings suggestive of emphysema were present in 67 cases and these were accompanied by a reduced M.E.F. in 31. *B. Golberg*

1144. **Mycobacterial Cervical Adenitis in Children**
S. D. Davis and G. W. Comstock. *Journal of Pediatrics* [*J. Pediat.*] **58**, 771–778, June, 1961. 21 refs.

It is becoming apparent that mycobacteria other than *Mycobacterium tuberculosis* may give rise to tuberculin sensitivity and to clinical illness, including cervical adenitis. The authors reviewed all cases of mycobacterial cervical adenitis in children recorded by the Muscogee County Tuberculosis Study, Columbus, Georgia, a total of 24 such cases having been seen since May, 1946. Acid-fast mycobacteria were recovered on culture from 11 children; in the others either closed lesions only were present or cultures were negative. Tuberculin testing was performed (often concurrently) with P.P.D.-S, P.P.D.-B (Battey strain), and P.P.D.-G (an antigen prepared from atypical mycobacteria). The reader of the reactions was unaware of the order of the tests at the time. The combined information available from the cultural characteristics and from the skin tests suggested that 17 of the 24 children were infected with one of the atypical mycobacteria. In 8 of these the colonies on culture were small and smooth—cream-coloured in 2 and orange or yellow in 6. None of the atypical group showed much sensitivity to P.P.D.-S.

It is concluded that in the area of the south-eastern United States from which these patients were drawn most cases of granulomatous cervical adenitis in children are not caused by *Myco. tuberculosis* but by atypical mycobacteria. The group at risk of such disease in the community were chiefly children 1 to 3 years of age; in a small-scale skin-testing survey with P.P.D.-G it was found that about 6% of pre-school children gave positive reactions. It is estimated that the annual attack rate among 1- and 2-year-old children cannot be more than 0·5%. *John Lorber*

Venereal Diseases

1145. **Application of the Immunofluorescence Method to the Serological Diagnosis of Syphilis.** (Application au diagnostic sérologique de la syphilis de la méthode d'immunofluorescence)

A. VAISMAN and A. HAMELIN. *Presse médicale* [*Presse méd.*] **69**, 1157–1159, May 27, 1961. 11 refs.

This paper from the Institut Alfred Fournier, Paris, reports a comparison of the results given by the fluorescent treponemal antibody (F.T.A.) test, the treponemal immobilization (T.P.I.) test, and a battery of standard tests for syphilis (S.T.S.), comprising the Kolmer W.R. with heart extract and cardiolipin antigens, and the Kahn, Kline, and Reiter tests, which were performed on 1,171 sera and 126 samples of cerebrospinal fluid (C.S.F.) The F.T.A. technique was based on that of Deacon *et al.* (*Proc. Soc. exp. Biol.* (*N.Y.*), 1957, **96**, 477; *Abstr. Wld Med.*, 1958, **24**, 26). Sera were tested at dilutions of 1:100 and 1:200 and C.S.F. either undiluted or diluted 1:10, 0·05 ml. being allowed to act on the treponemes for 30 minutes. After washing, 0·05 ml. of a commercially available goat antihuman globulin conjugate diluted to its optimum titre was applied for 30 minutes. Deacon's criteria of reactivity were followed.

The specificity of the F.T.A. test was assessed by testing 465 normal sera which had given negative results with the T.P.I. test and the S.T.S.; these were all found to be non-reactive in the F.T.A. test. Sera from a further 12 patients were thought to have given non-specific reactions with the S.T.S. because the T.P.I. and Reiter tests were negative; these also gave negative results in the F.T.A. test. Complete agreement was found between the F.T.A. and T.P.I. tests on 616 sera which were T.P.I.-positive and most of which gave positive results with lipoidal antigen tests. Quantitative F.T.A. tests were then performed on 78 sera from known cases of syphilis; the results suggested that the F.T.A. test became positive earlier than the other tests, and in 4 cases of dark-field positive primary syphilis it was the only test to give a positive result. Maximum titres were found in secondary syphilis; the titres tended to be lower in treated cases and in late syphilis. The F.T.A. test thus appeared to be more sensitive than the lipoidal antigen tests.

All of 67 specimens of C.S.F. from non-syphilitic patients gave a negative result by the F.T.A. test, as did also 6 specimens from syphilitic patients without evidence of involvement of the central nervous system. Samples of C.S.F. from 53 patients with various types of neurosyphilis all gave a positive result in the F.T.A. test, the highest titres being observed in patients with general paresis.

The authors suggest that the antibody detected by the F.T.A. test may differ from immobilizing antibody, basing this suggestion on the high sensitivity of the test in early syphilis, whereas immobilizing antibody usually first becomes demonstrable relatively late in the primary stage. In contrast, in late syphilis the titre in the T.P.I test is said to be higher than that of the F.T.A. test They conclude that it seems unlikely that the F.T.A. test will be of help in differentiating between the individual treponematoses, since fluorescence tests using *Treponema pallidum*, *T. pertenue*, and *T. cuniculi* as antigens all gave similar negative or positive results with normal and syphilitic sera. *A. E. Wilkinson*

1146. **Influence of Lysozyme upon the Treponeme Immobilization Reaction**

M. METZGER, P. H. HARDY JR., and E. E. NELL. *American Journal of Hygiene* [*Amer. J. Hyg.*] **73**, 236–244, March, 1961. 1 fig., 20 refs.

It has been reported that *Treponema pallidum* when freshly isolated from syphilitic lesions does not show reactivity with syphilitic sera in agglutination or immobilization tests; the organism becomes reactive only after incubation *in vitro*. This initial non-reactivity has been attributed to the presence of a non-antigenic capsule or slime layer on the organism. Histological studies of the mucoid material found in the early skin lesions of syphilis in rabbits have suggested that the capsular material may be similar to hyaluronic acid.

The effect of the enzymes hyaluronidase and lysozyme on the rate of immobilization of *T. pallidum* by syphilitic serum in the presence of complement was studied at Johns Hopkins University, Baltimore. Treponemes were incubated with 100 to 400 μg. of bovine testicular hyaluronidase per ml. of suspension for up to 10 hours before the addition of syphilitic serum and complement; no appreciable acceleration of immobilization occurred. This suggested that hyaluronidase was not the enzyme responsible for the development of the reactive state of treponemes. Lysozyme was found to have a very marked effect in accelerating immobilization. In the presence of 100 μg. of lysozyme per ml. a syphilitic serum immobilized 50% of the treponemes in 4 hours; without the enzyme this did not occur until the mixtures had been incubated for 10 hours. Treponemal immobilization (T.P.I.) tests are usually read after 18 hours' incubation at 35° C.; it was found that the titre of immobilization reached at this time could be produced after only 10 hours with added lysozyme. In tests carried out on 46 non-syphilitic sera there was no evidence of non-specific immobilization in the presence of 100 μg. lysozyme per ml. but when the lysozyme level was increased to 500 μg. per ml. the survival of the treponemes was appreciably reduced.

The authors consider that their results are consistent with the destruction of a non-antigenic mucopolysaccharide surface layer on treponemes by lysozyme. They suggest that the effect of higher concentrations of complement in increasing the sensitivity of the T.P.I. test may be due to the excess lysozyme contributed by the extra guinea-pig serum. *A. E. Wilkinson*

1147. **Investigation into the Treponemicidal Activity of Griseofulvin.** (Untersuchungen über treponemizide Wirkung von Griseofulvin)
T. MATNER. *Dermatologische Wochenschrift* [*Derm. Wschr.*] **143**, 492–495, May 13, 1961. 17 refs.

From the University Skin Clinic, Frankfurt am Main, the author describes the case of a patient with superficial trichophyton infection who was treated with griseofulvin. Since the appearance of this patient's teeth aroused some suspicion of congenital syphilis serological tests were performed. The result of the treponemal immobilization test showed that treponemicidal substances were present in the serum. However, when this test was repeated 2 weeks after administration of griseofulvin had been stopped it gave an entirely negative result. It was thought possible that griseofulvin might have been responsible for the treponemicidal effect observed and in view of the widespread use of this drug it was decided to investigate whether it had any effect on *Treponema pallidum in vivo* which could lead to the presence of syphilis being masked. To this end 4 patients with dark-field positive syphilitic lesions were given large doses of griseofulvin. It was found, however, that the drug had no influence on the recoverability of *T. pallidum* from the sores and did not promote healing of the syphilitic lesions. *G. W. Csonka*

1148. **Resistance of Gonococci to Penicillin**
INTERIM REPORT BY A MEDICAL RESEARCH COUNCIL WORKING PARTY APPOINTED TO EXAMINE THE RESISTANCE OF GONOCOCCI TO PENICILLIN. *Lancet* [*Lancet*] **2**, 226–230, July 29, 1961. 23 refs.

The authors of this report first review the incidence of gonococcal infection in Great Britain since 1946 and particularly since 1955 and discuss the sensitivity of the organisms to penicillin alone and penicillin in oil with 2% aluminium monostearate (P.A.M.). The investigation, the aim of which was to assess the pretreatment sensitivity of gonococci and to determine the sensitivity of these organisms from patients who had failed to respond to treatment, included only patients attending venereal disease clinics, and nine large laboratories participated in the study. The culture media used and the methods for assaying sensitivity *in vitro* are adequately outlined. Although identical techniques were not used at the various participating centres, suitable cross-checks were carried out to assure comparability of results.

The highest incidence of decreased sensitivity of gonococci to penicillin was observed in Sheffield and Wakefield and, for a part of the period, in one area in London. The survey covered the period August, 1959 to March, 1960, and a total of 1,984 strains were examined. Of 137 strains from patients who had not responded to treatment, 73 were inhibited *in vitro* by as little as 0·06 unit of penicillin per ml. or less, giving rise to the suspicion therefore that these were not cases of treatment failure but cases of reinfection. As reinfection during the first post-treatment week appeared to be unlikely, the results obtained with organisms persisting in spite of treatment or appearing in the first week after treatment were considered to be more significant. Of 38 such strains, 32 were sensitive only to 0·125 to 1·0 unit of penicillin per ml.; in these cases 1·2 mega unit of P.A.M. had proved ineffective. During the period of the study certain changes in the penicillin sensitivity of gonococci were noted; thus in Southampton and Manchester there was a decrease in the proportion of relatively resistant strains, but an increase in Birmingham, Liverpool, Wakefield, and Sheffield.

The suitability of sulphonamides for the short-term treatment of gonorrhoea is briefly considered. It is suggested that streptomycin should not be relied upon as a long-term substitute for penicillin because of the tendency for resistant strains to emerge. The emergence of penicillin-resistant strains, it is thought, may be a consequence of the use of slow-release penicillin preparations, since these produce a prolonged but comparatively low concentration of the antibiotic in the blood.
F. Hillman

1149. **Gonorrhea-like Syndrome Caused by Penicillin-resistant *Mimeae***
R. H. SVIHUS, E. M. LUCERNO, R. J. MIKOLAJCZYK, and E. E. CARTER. *Journal of the American Medical Association* [*J. Amer. med. Ass.*] **177**, 121–124, July 15, 1961. 18 refs.

As a consequence of alarming reports of an increase in " penicillin-resistant gonorrhoea " received from U.S. Naval units stationed in the Mediterranean area it was decided to investigate all cases of acute urethritis seen at the U.S. Navy Station Hospital, Naples, between October, 1960, and March, 1961. Of 42 such patients, 37 were found to have intra- and extra-cellular Gram-negative diplococci in the urethral discharge, which was purulent, and of these the discharge from 34 patients grew colonies resembling those of *Neisseria gonorrhoeae*. After subculture further identification in carbohydrate fermentation media showed that 12 of these patients were infected with *N. gonorrhoeae* and 22 with organisms of the *Mimea* species. (*Mimeae* were first isolated by DeBord from the genital and conjunctival tract in 1939 and were so named by him because of their ability to mimic *Neisseria* in morphology, staining reactions, and culture characteristics; however, they do not produce acid in glucose solution.) Antibiotic sensitivity tests showed that all strains of *N. gonorrhoeae* isolated were sensitive to penicillin whereas most of the strains of *Mimea* were penicillin-resistant. Clinically, the patients with *N. gonorrhoeae* infection responded readily to penicillin, but only 4 of the 22 patients infected with *Mimeae* did so satisfactorily, the remaining 18 subsequently responding to broad-spectrum antibiotics. This study thus does not support the concept of penicillin-resistant *N. gonorrhoea* infection.

[This is an interesting paper, which suggests that identification of *N. gonorrhoeae* by smear alone may not be justified. It is a pity that the penicillin-resistant " *Mimeae* " are not more fully characterized, and in particular the results of serological studies and epidemiological investigations would have been of great interest. Further work into the nature of the *Mimeae* and their relationship to " gonorrhoea " is indicated.]
G. W. Csonka

Allergy

1150. **Effect of Changes in Arterial pH on the Action of Adrenalin in Acute Adrenalin-fast Asthmatics**
J. S. BLUMENTHAL, M. N. BLUMENTHAL, E. B. BROWN, G. S. CAMPBELL, and A. PRASAD. *Diseases of the Chest* [*Dis. Chest*] **39**, 516–522, May, 1961. 14 refs.

After a number of preliminary experiments on dogs and guinea-pigs, the results of which are briefly described, adrenaline (10 to 25 μg. by drip) was administered intravenously to 2 healthy non-anaesthetized subjects at the University of Minnesota Medical School, Minneapolis, to determine the effect of the drug under conditions of acidosis (produced by inhaling 10% carbon dioxide in oxygen) and alkalosis (produced by voluntary hyperventilation). It was found that the heart rate was increased to a greater extent when the patients were in respiratory alkalosis (*p*H 7·6) than when in respiratory acidosis (*p*H 7·2). Of significance also were the more marked changes in the electrocardiogram, ventricular extrasystoles, and the T-wave noted during alkalosis.

These findings suggested to the authors that asthmatics may become adrenaline-fast because of respiratory acidosis, and 45 adrenaline-fast asthmatic patients were therefore given 120 to 300 ml. of 1 M sodium lactate intravenously over 30 minutes. Arterial blood *p*H values, obtained in 10 cases, ranged from 7·26 to 7·32 before therapy and from 7·39 to 7·45 after therapy. The results were good when the sodium lactate was given early, rapidly, and before the thick sputum became more important than the smooth-muscle spasm. It is suggested that the beneficial effect of the lactate may be due to an increased effect of the patient's endogenous adrenaline in a more alkaline medium. *G. B. West*

1151. **Repository-emulsion Treatment of Ragweed Pollinosis**
L. L. HENDERSON, H. M. CARRYER, L. E. PRICKMAN, G. A. KOELSCHE, and G. A. PETERS. *Proceedings of the Staff Meetings of the Mayo Clinic* [*Proc. Mayo Clin.*] **36**, 246–254, May 10, 1961. 5 refs.

The authors describe the results in 41 patients treated with an emulsion of ragweed pollen antigen made according to the method described by Brown (*Ann. Allergy*, 1959, **17**, 34), in which the ragweed extract is emulsified with an equal volume of an "arlacel"–"drakeol" mixture. It was calculated that after 300 cycles through an 18-gauge needle a good dispersed phase was obtained, although 1 to 2% of the antigen remained unemulsified as judged by size of skin response in sensitive subjects. The main purpose of the study was to avoid reactions and, when they did occur, to see whether they could be anticipated or explained. Therapeutic results were of secondary consideration in this study, but it was noted that the results were as good as those obtained with saline extracts; only one patient wanted to return to the multiple-dose treatment, and most of the others accepted emulsion therapy enthusiastically. It was assumed that if reactions had occurred with saline extracts, some type of reaction was likely with emulsion therapy; if there had been no reaction with saline, emulsion would cause little trouble. Two injections, a month apart, of 4,800 and 12,600 protein nitrogen units (P.N.U.) respectively caused fewer reactions than a single injection of 12,600 P.N.U.; only one patient had a severe reaction. It is planned in 1961 to continue and expand repository treatment.

[Brown would now consider that an emulsion which contained any free antigen should not be used. Improved techniques have eliminated reactions.]
A. W. Frankland

1152. **Further Study of Effectiveness of New Antihistaminic Drugs in Ragweed Pollinosis**
A. L. SCHWANDT, H. W. WAHNER, and G. A. PETERS. *Proceedings of the Staff Meetings of the Mayo Clinic* [*Proc. Mayo Clin.*] **36**, 261–267, May 24, 1961. 4 figs., 2 refs.

A double-blind trial of four new antihistaminic drugs in which 20 patients with pollinosis took part is described.

The drugs were "forhistal" (dimethpyrindene maleate), IR 157 (N-[*p*-chlorbenzhydryl oxyethyl]-nortropine), R 1575 (a tertiary amine), and "algic" (a compound of racephedrine hydrochloride, phenyltoloxamine dihydrogen citrate, and chlorpheniramine maleate). These were compared with ephedrine sulphate and chlorpheniramine. Evaluation of the drugs was based on cards filled in daily by the patients on which they graded their symptoms, degree of exposure, number of tablets taken, and response to treatment. Each drug was taken for 2 successive days in rotation. The data thus obtained showed that none of the drugs was outstanding, but that most of them helped patients with mild symptoms. Chlorpheniramine was the most effective antihistaminic, but ephedrine sulphate, surprisingly, appeared to afford little relief. It is noted that there was a definite correlation in the 1960 ragweed season between the weather data, pollen counts, and patients' symptoms.
A. W. Frankland

1153. **The Newer Anti-allergic Agents.** [Review Article]
R. E. WILHELM. *Medical Clinics of North America* [*Med. Clin. N. Amer.*] **45**, 887–906, July, 1961. 3 figs., bibliography.

1154. **The Nature and Properties of Antibodies in Sera of Allergic Individuals. A Review**
L. GYENES and A. H. SEHON. *International Archives of Allergy and Applied Immunology* [*Int. Arch. Allergy*] **18**, 330–347, 1961. 1 fig., bibliography.

Nutrition and Metabolism

1155. **Lysine and Potassium Supplementation of Wheat Protein**
L. A. BARNESS, R. KAYE, and A. VALYASEVI. *American Journal of Clinical Nutrition* [*Amer. J. clin. Nutr.*] **9**, 331–334, May–June, 1961. 40 refs.

Much of the work on amino-acid supplementation of diets has been done with experimental animals and very little with man. The investigation reported here was carried out at the Driscoll Foundation Children's Hospital, Corpus Christi, Texas, on 22 male infants aged 3 to 17 months who had been admitted for severe diarrhoea and were investigated at least 15 days after they had recovered.

Balance measurements were carried out on a range of experimental diets all based on wheat or wheat and milk. The range of Calories and protein fed was 75 to 120 and 1·2 to 4 g. respectively per kg. body weight per day. The diets were supplemented with lysine or potassium or both. Each dietary period lasted 9 days, and each infant was studied for 3 to 6 such periods. Urine and faeces were collected for analysis, and specimens of blood were analysed at the beginning and end of the experiment.

The results showed that the nutritional value of wheat protein as measured by nitrogen balance was considerably improved by supplementation with lysine and potassium. Wheat supplemented with lysine and potassium had a nutritional value close to that of milk and was an adequate source of protein for growing infants over the periods studied. Supplementation with lysine alone without potassium was not effective in improving the value of wheat protein. Again, the lysine and potassium were effective only when mixed with the wheat diets and not merely given as separate supplements. *John Yudkin*

1156. **Metabolic Studies on Large and Small Eaters**
G. A. ROSE and R. T. WILLIAMS. *British Journal of Nutrition* [*Brit. J. Nutr.*] **15**, 1–9, 1961. 21 refs.

Why do some people eat more than others? Two men may weigh the same and have a similar work output, yet one may eat twice as much as the other. The authors of this paper from Paddington General Hospital, London, have studied the oxygen uptake of 6 pairs of young men selected to differ as widely as possible in caloric intake but as little as possible in body weight. The group of large eaters had a nominal caloric intake almost double that of the small eaters. The oxygen uptakes were measured basally and during a variety of standard and free-style exercises, and also after a standard meal.

There was a wide scatter between individuals in the various values for oxygen consumption. The mean "basal" oxygen consumption was identical in the two groups. The increments due to standing and sitting were generally small and differed little between the two groups. A weight-raising exercise showed some variation between subjects, but on the average the two groups behaved similarly. This was also true of the step test, which involved walking and climbing at a standard rate. The remaining two exercises were carried out free-style and the subject was advised to choose his own "natural" pace. The small eaters used less oxygen in relation to time, but a similar amount in relation to distance covered. In fact the criterion by which the two groups could be most clearly distinguished was the walking rate at which the subjects chose to do the test. The mean rate of the large eaters was 3·35 miles (5·39 km.) per hour, as compared with 2·92 miles (4·69 km.) per hour for the small eaters. The likelihood of the observed differences arising by chance is stated to be less than 1%. In the final exercise, walking up and down stairs, the small eaters again tended to be slower movers. They accomplished their work at an oxygen cost (over their standing rates) of 6% less than the large eaters.

The specific dynamic action of a standard meal was also similar in the two groups, and it was concluded that the differences in their caloric intakes were not due primarily to any constitutional differences in energy requirements.

Since the large eaters had natural rates of walking consistently faster than those of the small eaters, it is suggested that this may be an index of a general restlessness and pace of activity which may be related to their large food intake. *A. G. Mullins*

1157. **Reducing Diets. Weight Loss of Obese Patients on Diets of Different Composition**
R. F. FLETCHER, M. Y. MCCRIRICK, and A. C. CROOKE. *British Journal of Nutrition* [*Brit. J. Nutr.*] **15**, 53–58, 1961. 21 refs.

At Little Bromwich General Hospital, Birmingham, 6 women with simple obesity who were in-patients in a metabolic ward and under close supervision were given diets providing 800 Calories daily in which most of the calories were derived from carbohydrate, protein, or fat respectively. A basic diet of 500 Calories a day was supplemented by 300 Calories per day as protein ("casilan"), butter, or sugar given with 3 methylcellulose biscuits. The total duration of the experiment was 7 to 10 weeks, during 6 weeks of which each patient received the three supplements separately in turn for 14 days each.

Statistical analysis showed no significant difference in the rate of loss of weight on the different diets. There was a positive correlation between the loss of weight and the initial weight. *A. G. Mullins*

1158. **Hypocholesterolemic Agents.** [Review Article]
R. H. FURMAN and C. W. ROBINSON. *Medical Clinics of North America* [*Med. Clin. N. Amer.*] **45**, 935–959, July, 1961. 1 fig., bibliography.

Gastroenterology

1159. **Mucosal Tears at the Oesophagogastric Junction (the Mallory–Weiss Syndrome)**
M. Atkinson, M. B. Bottrill, A. T. Edwards, W. M. Mitchell, B. G. Peet, and R. E. Williams. *Gut* [*Gut*] 2, 1–11, March [received May], 1961. 10 figs., 21 refs.

The authors describe 11 cases of the Mallory–Weiss syndrome seen at St. James's Hospital, Leeds, and Halifax General Hospital. The diagnosis was established at necropsy in 7 patients, at laparotomy in 2, and at gastroscopy in 2. In 8 patients the presenting symptom was gastro-intestinal haemorrhage; of the remaining 3 patients, in whom there was little or no bleeding, mediastinitis developed in 2. Vomiting occurred in 3 patients 30 minutes to 3 hours before the haematemesis. None of the patients, all of whom were over 49, was a chronic alcoholic. Atrophic changes were seen at gastroscopy in one patient; 4 patients had a small hiatus hernia, while in 3 coughing, status asthmaticus, and epileptic convulsions may have been contributory factors. There were 7 deaths, 5 being due to the mucosal tear at the cardia. Of the remaining 4 patients, 2 recovered with conservative treatment and 2 after suture of the tear at operation.

Experimentally raising the intragastric pressure by air distension to 150 mm. Hg in 6 cadavers caused mucosal tears in all. In healthy subjects gastric pressures up to 200 mm. Hg were observed during retching, while the intra-oesophageal pressure ranged from 35 to 50 mm. Hg. Hence retching in a subject in whom the cardia enters the thorax (as in hiatus hernia) may be associated with pressure of the order necessary to cause tearing.

The authors state that mucosal tears were found in 4 out of 73 consecutive patients admitted to hospital for gastro-intestinal haemorrhage. They suggest that when at operation for such haemorrhage no cause can be found the stomach should be opened and the cardia inspected.

G. L. Asherson

1160. **Certain Functional and Morphological Changes in the Liver Deprived of Portal Blood.** (Некоторые функциональные и морфологические изменения печени при лишении ее портальной крови)
M. V. Rudenskaja and Ê. I. Gal'perin. *Советская Медицина* [*Sovetsk. Med.*] 25, 105–112, April, 1961. 6 figs., 16 refs.

Reports in the literature on the subject of changes in the liver deprived of portal blood are scarce and contradictory. The authors have observed 18 patients with radiologically demonstrated portal block due to various forms of thrombotic and phlebitic complications. The insufficiency of the collateral circulation was confirmed by the high pressure in the portal vein (410 mm. Hg). In spite of this, however, the blood total proteins, protein fractions, fibrinogen, prothrombin, urea, residual nitrogen, amino-acid, bilirubin, and cholesterol concentrations were, in the great majority of patients, within normal limits. Death in most cases was due to severe anaemia resulting from bleeding oesophageal varices.

In a series of experimental studies end-to-side portacaval anastomosis was performed on 22 dogs. Of these, 2 died soon after the operation, but the remainder were followed for up to 3 years. During the first year there was evidence of haemodynamic disturbances and of atrophic and dystrophic changes in the liver, but during the subsequent 2 years the liver morphology returned to normal except for some focal fatty infiltration and storage of haemosiderin in Kupffer's cells and macrophages. The liver cells were normal in appearance; the hepatic lobular structure was lost in places, but there were also areas of regeneration, while at the same time the serum protein levels returned to normal.

S. W. Waydenfeld

1161. **Hepatic Coma.** [Review Article]
S. Sherlock. *Gastroenterology* [*Gastroenterology*] **41**, 1–8, July, 1961. 2 figs., 46 refs.

STOMACH AND DUODENUM

1162. **Effect of Medical and Surgical Vagotomy on the Augmented Histamine Test in Man**
I. E. Gillespie and A. W. Kay. *British Medical Journal* [*Brit. med. J.*] 1, 1557–1560, June 3, 1961. 3 refs.

At the Royal Infirmary, Sheffield, 40 male patients with proved duodenal ulcer were selected for vagotomy and gastroenterostomy. Before operation each patient was given two augmented histamine test meals, one plain and the other after "medical vagotomy" produced by giving an intramuscular injection of 50 mg. of hexamethonium bromide with 0·325 mg. of atropine sulphate. At unstated intervals after operation the test meals were repeated. Complete aspiration of the gastric juice was ensured by an electric suction pump which was "frequently interrupted" by injecting air to maintain patency. After a 12-hour fast four 15-minute aspirates were collected, 100 mg. of an antihistamine (mepyramine maleate) was given intramuscularly, and after 30 minutes 0·04 mg. of histamine acid phosphate per kg. body weight was injected subcutaneously.

The variation in gastric acid output was considerable, ranging (after omitting unsatisfactory tests) from 10·2 to 30·7 mEq. in 30 minutes before vagotomy, and from 0 to 17·7 mEq. in 30 minutes after it. [There is no analysis or discussion of this variation.] In the 36 cases in which the tests were technically satisfactory the correlation between the reduction in acid output after medical and surgical vagotomy was significant ($r=0{\cdot}4783$, $t=3{\cdot}176$, $P<0{\cdot}01$). [The statistical procedure employed is based on the assumption that the experimental error in the

first estimate is evenly distributed and not too large in comparison with the reduction produced by vagotomy; the abstracter does not accept this.] The average reduction in acid output after gastroenterostomy and vagotomy was 58·5%, and after medical vagotomy seems to have been between 40 and 45% [though this is not stated in the paper]. The greater reduction after surgical vagotomy is attributed to the gastroenterostomy.

The period of clinical follow-up ranged from 6 months to 4 years, and so far 2 patients have developed recurrent ulcers. In one of these the postoperative tests indicated that vagotomy was incomplete and in the other the reduction after medical vagotomy was only 16% and after surgical vagotomy 20%. The authors suggest, "although there is no valid mathematical support for a separation", that patients with duodenal ulcer can be divided by medical vagotomy into two groups, in one of which the acid secretion is insufficiently reduced by vagotomy, so that antrectomy should also be performed. The suggested dividing point is that at which medical vagotomy produces less than 35% reduction in acid output.

[If these 40 cases are representative, it means that about two-thirds of male duodenal ulcer patients are suited to vagotomy and gastroenterostomy, whereas the remaining third should also undergo antrectomy. Possibly in another 5 years the follow-up of this series will show whether the authors are right, and whether the majority of recurrent ulcers fall in the 35% of cases in which augmented histamine test meals showed less than average reduction in acid output after hexamethonium and atropine.] *Denys Jennings*

1163. **Endoscopic Examination of the Stomach and Duodenal Cap with the Fiberscope**
B. I. HIRSCHOWITZ. *Lancet* [*Lancet*] **1**, 1074–1078, May 20, 1961. 13 figs., 2 refs.

The author of this paper from the University of Alabama Medical Center, Birmingham, Alabama, describes his experience of the "fiberscope", which consists of a flexible bundle of glass fibres, in examination of the oesophagus, stomach, and duodenum. The principal merits of the instrument are that it is easy to use both in the wards and in the out-patient clinic and, because of its flexibility, causes no discomfort during passage or afterwards. Light transmission is good.

The appearances of the normal duodenal bulb and the bulb in cases of chronic duodenal ulcer are described and illustrated. The value of the instrument in detecting haemorrhage from an acute duodenal ulcer is discussed. The author considers that the fiberscope has "already reached the stage where it should replace the conventional gastroscope". *I. McLean Baird*

1164. **The Secretory Background to Gastric Ulcer**
P. A. J. BALL. *Lancet* [*Lancet*] **1**, 1363–1365, June 24, 1961. 5 figs., 13 refs.

Gastric secretory activity was studied in 50 patients (29 men and 21 women) with gastric ulcer at the Royal Infirmary, Cardiff, samples of gastric juice being taken every half-hour between 8.30 p.m. and 7.30 a.m. and the gastric secretion collected for 45 minutes after a dose of 0·4 mg. of histamine per 10 kg. body weight. In all the patients the gastric contents remained acid so long as food was present in the stomach. In general, the samples became neutral or alkaline when the ulcer was in the body of the stomach; they did not do so when the ulcer was in the antrum. Patients with antral ulcers tended also to secrete a large quantity of acid in response to histamine, although the concentration of acid was not closely related to the actual quantity of acid secreted.

Patients in whom the gastric juice became neutral during the night secreted acid at a lower concentration after histamine than those in whom gastric juice remained acid. The author suggests that nocturnal neutralization may be due to either a diminished secretion of acid or an excessive secretion of an alkaline component in gastric juice. This is in accord with the theory that the parietal cells secrete acid at a fixed concentration which is diluted or neutralized by an alkaline component secreted by the other gastric cells. *Thomas Hunt*

1165. **The Histological Background to Gastric Ulcer**
P. A. J. BALL and A. H. JAMES. *Lancet* [*Lancet*] **1**, 1365–1367, June 24, 1961. 2 figs., 12 refs.

A comparative study was carried out at the Royal Infirmary, Cardiff, of the histological appearances of the gastric mucosa of resected stomachs and the secretory behaviour determined before operation. From 25 of the 50 patients investigated by Ball [see Abstract 1164] who were later subjected to partial gastrectomy, nocturnal samples of gastric juice were obtained and histamine tests were carried out. The state of the gastric epithelium and the antral glands was assessed histologically and the presence or absence of intestinal metaplasia noted. Neither of the observers knew from which patient or from which part of the stomach the histological material came. The mucosa was sectioned from the antrum and from the greater curvature, both sites being at least 2 inches (5 cm.) away from any ulcer that was present. In general, patients with nocturnal neutrality frequently showed histological abnormality, while those with acid nocturnal gastric juice and antral ulcers much more often had a normal gastric mucosa.

The main abnormalities noted were a reduction in height of the epithelial cells and a lack of the large extracellular mucus droplets which are normally found in healthy mucosa. The authors suggest that since mucus is soluble in alkali or neutral solutions but is precipitated as a gel in acid solutions, neutral gastric juice prevents the normal layer of mucus forming on the surface and so allows the protective mucus barrier to be weakened or removed. *Thomas Hunt*

1166. **Factors Influencing Mortality in Bleeding Peptic Ulcer. I. The Presence of Serious Complicating Illness**
W. F. MITTY, F. J. BREEN, R. WALLACE, and W. J. GRACE. *American Journal of Digestive Diseases* [*Amer. J. dig. Dis.*] **6**, 389–394, May, 1961. 14 refs.

In a series of three papers [see Abstracts 1167 and 1168] the authors have examined some of the factors which appear to have affected the mortality rate in a

group of 421 patients admitted to St. Vincent's Hospital, New York, with gastro-intestinal haemorrhage from proven peptic ulcer. The total number of deaths was 49 (11·4%), 37 of which occurred in patients treated medically, no fewer than 31 of whom had serious complicating disease. In 3 patients death followed elective gastrectomy and in 9 others emergency gastrectomy.

The first of the three papers is concerned with the importance of complicating disease in its effect on prognosis in the light of these figures. The only 2 deaths in patients under 40 years of age were associated with hepatic cirrhosis and chronic glomerulonephritis. In patients over the age of 40, as might be expected, cardiovascular disease was the most important complication, and the mortality rate in all patients suffering from serious cardiac lesions was therefore compared with the mortality rate in those without such lesions. For all age groups the mortality rate was 6·6% in patients without cardiac disease compared with 36·8% in those with this complication. *T. D. Kellock*

1167. **Factors Influencing Mortality in Bleeding Peptic Ulcer. II. The Occurrence of Massive Hemorrhage**
W. F. Mitty, F. J. Breen, R. Wallace, and W. J. Grace. *American Journal of Digestive Diseases* [*Amer. J. dig. Dis.*] **6**, 395–399, May, 1961. 7 refs.

In the second paper in this series [see Abstracts 1166 and 1168] the relationship between the severity of the haemorrhage and mortality is discussed. No satisfactory correlation was found between the mortality rate and such factors as the presence or absence of shock, the haemoglobin level, haematocrit value, pulse rate, or blood pressure, but there was a correlation between mortality and the amount of blood transfused. In view of the finding that the presence of cardiac disease profoundly affected the mortality rate patients with this complication were considered separately from those without. In both groups the mortality rate rose sharply with the amount of blood transfused, but patients with a cardiac lesion, as expected, fared very much worse; 21 out of 27 cardiac patients requiring one litre or less of blood in the first 24 hours survived, while of 5 patients who required over one litre all died.

The authors consider that this inability to stand major changes in blood volume is probably the biggest factor in the increased mortality in patients with cardiac disease and also in those of advanced age.
T. D. Kellock

1168. **Factors Influencing Mortality in Bleeding Peptic Ulcer. III. Emergency Gastrectomy; Comment on the Management of Patients with Bleeding Ulcer**
W. F. Mitty, F. J. Breen, R. Wallace, and W. J. Grace. *American Journal of Digestive Diseases* [*Amer. J. dig. Dis.*] **6**, 400–404, 1961. 3 refs.

In the third paper [see Abstracts 1166 and 1167] the authors consider emergency gastrectomy in relation to mortality in peptic ulcer. Of 20 patients subjected to gastrectomy, 6 died, including 4 with severe heart disease.

The authors' general conclusions are that in patients below the age of 45 with bleeding ulcers and without serious complicating disease the prognosis is good and emergency surgery is rarely required. Conservative treatment should be given to patients over 45 if they are otherwise in good health until it is recognized that they need blood transfusion at a rate over 3 litres in the first 48 hours when emergency gastrectomy should be carried out. In patients over 70 and those with complicating illnesses the prognosis is poor, since they cannot tolerate blood loss of any magnitude. Early emergency gastrectomy may help to reduce the mortality in this group.

[The general conclusions in these three papers will be shared by most of those who are concerned with this problem. Unfortunately the small numbers in some of the groups and the omission of data relating to sex, site of ulcer, and to a lesser extent of age make it very difficult to compare this series with others.] *T. D. Kellock*

1169. **Long-continued Inhibition of Gastric Secretion by Poldine Methosulphate in Patients with Peptic Ulcer**
A. H. Douthwaite, T. H. Hills, and J. N. Hunt. *British Medical Journal* [*Brit. med. J.*] **1**, 1575–1579, June 3, 1961. 3 figs., 9 refs.

The effect of poldine methosulphate (" nacton ") in peptic ulcer and long-standing dyspepsia (mean duration 10 years) was studied in 16 male patients at Guy's Hospital, London, who after discharge were seen at regular intervals for 3 years or more. In one patient the diagnosis was proved to be wrong, while another did not take the drug regularly; these 2 patients were excluded from the trial.

During poldine administration there was complete freedom from dyspepsia in 83% of the 429 months at risk; in all patients the symptoms were relieved and the amount of antacids needed was reduced. Before treatment the average loss of working time was 4 weeks a year per patient, but during treatment this was reduced to *nil* in all except 3 patients who lost only a total of 20 working days during the 3-year period. Test meals to determine the response to glucose were carried out at regular intervals when the patients were taking dummy tablets or poldine; the dose of the latter was gradually increased to just below that which produced side-effects. There was half as much secretion of the acid parietal component during poldine therapy as during administration of dummy tablets, but the drug appeared to be no more effective in the hypersecretors. Secretion of the non-parietal component was reduced by only 22%. The drug had no effect on gastric emptying time.

Radiologically, the deformity of the duodenal cap decreased in 6 patients, presumably because of reduction in spasm, and this group had significantly more months free from dyspepsia than the 8 in whom the duodenal cap remained unchanged.

The authors recommend that poldine should be given 4 times a day, and the dose increased gradually almost to the level at which side-effects are produced. It may take 21 days for the full effect of the drug on gastric secretion and on symptoms to become apparent. They stress that poldine does not completely abolish dyspepsia in all patients, especially after overwork, but symptoms then respond to antacids. *A. Gordon Beckett*

Cardiovascular System

1170. **Fibrinolysin Therapy of Thromboembolism: Three Years' Experience**
A. L. Sheffer, S. Lisker, and P. Nemir Jr. *Angiology* [*Angiology*] **12**, 165–168, May, 1961. 16 refs.

This communication from the Graduate Hospital of the University of Pennsylvania, Philadelphia, describes the use of a thrombolytic agent, " actase ", a preparation of plasmin prepared by streptokinase activation of plasminogen, in the management of thromboembolic disease. Included in the trial were 67 patients suffering from pulmonary embolism (8), thrombophlebitis (26), arterial occlusion (22), and retinal vascular disease (11). The fibrinolysin dosage varied with the reduction in toxicity as more refined preparations became available, the eventual dosage regimen being 200,000 units dissolved in 200 ml. of saline infused over 2 hours for 3 days. Concomitant anticoagulant therapy was given in the form of heparin, 100 mg. intravenously every 12 hours.

No haemorrhagic complications were encountered. Four-fifths of the patients had a rise in temperature, but usually by less than 2° F. (1·1° C.), 2 to 6 hours after the infusion. There were no hypersensitivity reactions. In 2 cases in which the infusion fluid inadvertently infiltrated the subcutaneous tissue there was superficial cellulitis.

Though the authors report " a few encouraging examples in each group ", they conclude that " it will still be necessary to treat many more cases before a more definite impression can be expressed concerning the role of fibrinolysin in thromboembolic therapy ".

[There were no simultaneous controls in this study.]

A. S. Douglas

1171. **Hardness of Local Water-supplies and Mortality from Cardiovascular Disease in the County Boroughs of England and Wales**
J. N. Morris, M. D. Crawford, and J. A. Heady. *Lancet* [*Lancet*] **1**, 860–862, April 22, 1961. 13 refs.

Following work in Japan by Kobayashi, Schroeder in the U.S.A. reported (*J. Amer. med. Ass.*, 1960, **172**, 1902; *Abstr. Wld Med.*, 1960, **28**, 415) the finding of a highly significant negative correlation between average hardness of drinking water and mortality from cardiovascular disease in various States. The present preliminary communication describes a similar investigation, based on official figures, for the county boroughs of England and Wales. About one-third of the total population lives in these towns and differences in regard to cardiovascular mortality among them are well recognized. Correlations were calculated between (1) death rates from 38 causes and groups of causes of death " in 170 sex–age brackets ", and (2) the indices of average hardness of the local water supply as delivered in the 83 county boroughs. The tables presented show marked correlations, all negative, between water hardness and total cardiovascular mortality, that is, the softer the water, the higher the mortality. Correlations between hardness and non-cardiovascular deaths were small, except that for bronchitis, while the correlation with diabetes was negligible and that with chronic nephritis irregular.

In discussion the authors note that softness of the water may not be the direct cause of the high death rate from cardiovascular diseases; the latter may be associated with environmental, social, and other conditions. However, that there does seem to be a specific relationship between water hardness and cardiovascular mortality was shown among the other 51 towns when Lancashire, the West Riding of Yorkshire, and South Wales (the areas showing the highest correlations) were excluded. Correlations between water hardness and local climatic conditions are now being assessed. Work on the constituents of the water show that correlations with cardiovascular mortality are high for calcium content, contrasting remarkably with that of magnesium. It is pointed out that all data in this report refer to mortality only; morbidity and incidence require further study.

J. M. Browne Kutschbach

DIAGNOSTIC METHODS

1172. **" Nonspecific " ST and T-Wave Changes**
C. K. Friedberg and A. Zager. *Circulation* [*Circulation*] **23**, 655–661, May, 1961. 5 refs.

In an attempt to determine whether a more precise interpretation could not be made of electrocardiograms (ECGs) showing only ST-segment depression and T-wave inversion without other characteristic changes the authors have reviewed and correlated with the patients' clinical status 1,000 ECGs recorded at Mount Sinai Hospital, New York, records from patients with abnormalities of rhythm being excluded. In this series they found 209 examples showing ST-segment depression and T-wave inversion—changes usually characterized as " non-specific ". Of these 209 patients, 46 had received digitalis, 57 had had a recent acute episode of cardiac pain of variable duration, 57 suffered from some condition that could be held responsible for the changes, and in 49 there was no apparent cause for the ST–T abnormalities. In this last group the ST-segment and T-wave changes were of minimal degree and possibly insignificant.

In the group with cardiac pain ST depression invariably measured more than 0·5 mm. and T-wave inversion more than one mm. in depth, when combined, while isolated T-wave inversion was greater than 2 mm. and often 5 mm. in depth in the mid-precordial leads. There was no difference between the ECG tracings of the 22 patients with recent cardiac pain of less than half an hour's duration and those from the 35 patients with such pain lasting more than half an hour, provided

those with Q-wave changes (indicating transmural infarction) were omitted. It is therefore concluded that the ECG does not appear to distinguish between subendocardial ischaemia and subendocardial necrosis.

T. Semple

1173. **The Correlation of Electrocardiographic and Ballistocardiographic Changes in Chronic Pulmonary Disease.** (О взаимоотношении типа электрокардиограммы и изменений баллистокардиограммы у больных хроническими легочными заболеванилми)

Ju. A. Panfilov. *Терапевтический Архив* [*Ter. Arh.*] 33, 49–54, May, 1961. 2 figs., 11 refs.

The author points out that whereas the electrocardiogram (ECG) provides information only as to the electrical processes in the myocardium, ballistocardiography is a guide to its contractile function. In the present study the 75 patients investigated, of whom 39 had bronchial asthma, 11 pneumosclerosis, 7 bronchiectasis, and 5 abscess of the lung, while all had emphysema and chronic bronchitis, were, on the strength of the ECG findings, divided into two groups as follows: (1) 35 patients with right axis deviation; and (2) 40 patients with left axis deviation or a normal ECG. Ballistocardiographic investigation of Group 1 showed a normal or only slightly altered tracing (Brown's Grades I or II), indicating satisfactory contractability and great compensatory possibilities of the right ventricle. In all but 4 patients in Group 2, however, the ballistocardiographic tracings were grossly changed (Brown's Grades III or IV). Here the pulmonary disease was associated with advanced coronary atherosclerosis and myocardiosclerosis. All the patients were in circulatory failure of Grade II or III, the function of the right ventricle being grossly interfered with, the contractability of the myocardium impaired, and decompensation evident.

S. W. Waydenfeld

CONGENITAL HEART DISEASE

1174. **A Simple Isotope Dilution Technique for Quantitative Determination of Left to Right Shunts**

K. Amplatz, J. Marvin, P. Winchell, G. Gomez, P. Adams, and R. G. Lester. *American Journal of Roentgenology, Radium Therapy, and Nuclear Medicine* [*Amer. J. Roentgenol.*] 85, 1053–1058, June, 1961. 3 figs., 11 refs.

From the University of Minnesota Hospitals, Minneapolis, the authors describe the use of radioactive methyl iodide vapour for the detection of left-to-right intracardiac shunts. The technique is based on the principle that, following inhalation of a radioactive tracer gas into the lungs and hence into the left atrium, samples of blood taken simultaneously from the right heart by means of a cardiac catheter will show the appearance of radioactivity both sooner and in greater quantity when a left-to-right shunt is present than when no such lesion exists. That such a shunt is present is shown by the shorter appearance time of radioactivity in the right heart samples, while the site of the shunt may be demonstrated by successive repetitions of the test with the catheter lying in different positions in the right heart; further, its size can be computed from a comparison of simultaneous curves obtained by sampling blood from the pulmonary and femoral arteries.

Using this technique, the authors have investigated 105 patients with congenital heart disease. In 13 of these patients the test with radioactive methyl iodide demonstrated the presence of a left-to-right shunt which was too small to be detected by oximetry studies. The majority of these 13 patients had small ventricular septal defects. In 2 cases, however, the methyl iodide test failed to show a left-to-right shunt which was detectable by oximetry; in these cases a bidirectional shunt was present and the failure of the method can probably be explained by inaccurate positioning of the sampling catheter.

M. Harington

1175. **The Methyl Iodide Test in Left to Right Shunts: Technical Considerations**

K. Amplatz, J. F. Marvin, M. K. Loken, and W. D. Miller. *American Journal of Roentgenology, Radium Therapy, and Nuclear Medicine* [*Amer. J. Roentgenol.*] 85, 1059–1062, June, 1961. 4 figs., 2 refs.

This second paper [see Abstract 1174] deals with the technical aspects of the use of radioactive methyl iodide for the detection of left-to-right cardiac shunts. The gas can be easily prepared by simply adding a few drops of stable methyl iodide to a solution of ^{131}I-labelled sodium iodide and keeping the mixture in a glass bottle with a rubber stopper, through which samples of radioactive methyl iodide vapour can be withdrawn at will. Methyl iodide is highly soluble in fats, rubber, plastics, and lubricants and it has therefore been found necessary to store the doses used for inhalation (usually in volumes of 1 ml.) in stainless steel tubing closed by stopcocks with a special silicone lubricant. The gas is administered to patients by blowing air through this tubing and into the patient's nose or mouth at the beginning of inspiration.

The size of dose necessary was found to be 5 to 8 μc. per inhalation. The methyl iodide is rapidly absorbed by the lungs and hydrolysed in the body to inorganic iodide. Very little radioactivity is exhaled again by the patient and there is a correspondingly small radiation hazard to the attending personnel. If the patient's thyroid gland is blocked by previous administration of stable iodide the radioactivity absorbed can be recovered quantitatively in the urine, the biological half-life being about 6 hours.

The authors conclude that the radioactive methyl iodide test is a simple and sensitive means for detecting small left-to-right circulatory shunts. *M. Harington*

1176. **Regional Pulmonary Blood Flow in Patients with Circulatory Shunts**

C. T. Dollery, J. B. West, D. E. L. Wilcken, J. F. Goodwin, and P. Hugh-Jones. *British Heart Journal* [*Brit. Heart J.*] 23, 225–235, May, 1961. 10 figs., 8 refs.

The rate of clearance of radioactive carbon dioxide from the alveolar air space is a measure of the pulmonary blood flow. This clearance can be determined

for both the upper and lower pulmonary zones simultaneously and gives some idea of the distribution of blood flow through the lungs. In carrying out the method carbon dioxide labelled with radioactive oxygen (^{15}O) is inhaled and the breath held for 10 to 15 seconds. Pairs of scintillation counters arranged in front of and behind the chest measure the changes in radioactivity. The clearance rate of the gas is calculated from the rate of fall of the counting rate during breath holding after allowance has been made for background radiation and radioactive decay. Carbon dioxide is removed exponentially and the clearance rate is expressed as the percentage per second of the instantaneous activity. One pair of counters was placed over the left second rib 3 inches (7·5 cm.) from the midline and the other over the right lung 4 inches (10 cm.) lower down (7·5 to 8·75 cm. lower for children). With the counters in these positions the mean clearance values in 5 healthy young adults were 4·8% per second in the upper zone and 23·5% per second in the lower zone, giving a ratio of 0·2:1.

At Hammersmith Hospital (Postgraduate Medical School of London) the pulmonary clearance rates were then measured by this method in 15 patients with congenital cardiac lesions, of whom 4 had an atrial septal defect, 7 a ventricular septal defect, and 4 a patent ductus arteriosus; all had previously undergone a complete haemodynamic investigation. In some of the patients the pulmonary resistance was high while in some it was low. These two groups showed a big difference in isotope clearance rates, but no significant difference in the mean upper:lower zone ratios, which were 0·80 and 0·88 respectively. Such a ratio represents a greater upper zone blood flow than in the normal subject (ratio 0·2), but the explanation for this increase may not be the same in the two groups. The only patient showing a steep inversion of the normal ratio (4·04) was found at operation to have mitral stenosis, so that this finding was in accord with previous evidence available from patients with mitral stenosis. The authors state that by studying the size and shape of the " recirculation hump " on the tracings from the counters some idea of the size of the shunt can be obtained. This correlates fairly well with estimations made by the dye dilution and Fick methods and the technique described may well be more convenient in certain circumstances. *G. Clayton*

1177. **EEG Changes in Children Suffering from Congenital Heart Disease. Influence of O_2 Inhalation**
I. Lesný, I. Bor, and V. Vlach. *Electroencephalography and Clinical Neurophysiology* [*Electroenceph. clin. Neurophysiol.*] **13**, 173–179, April, 1961. 2 figs., 12 refs.

The authors report from the Charles University, Prague, that an abnormal amount of generalized asynchronous slow activity was noted in the encephalograms (EEGs) of 29 out of 34 children with cyanotic congenital heart disease and in 44 of 61 children with similar but acyanotic disease. The patients' ages ranged from 16 months to 17 years, but the incidence of EEG abnormalities proved to be unrelated to age. It was then found that the inhalation of 95% oxygen with 5% carbon dioxide for 3 minutes led to a shift towards a faster spectrum of EEG activity in 70% of the patients and in the majority this was sufficient to bring the record within normal limits. This effect usually began after 20 to 30 seconds; in some cases it continued for up to 30 seconds, while in others it persisted to the end of the period of inhalation. Except that its effect tended to be more prolonged in the cyanotic than in the acyanotic patients, no other significant difference in the response to oxygen could be demonstrated between these two groups.
L. G. Kiloh

1178. **Costal Erosion in the Tetralogy of Fallot.** (Les érosions costales dans la tétralogie de Fallot)
P. Soulié, P. Vernant, P. Leborgne, and P. Baledent. *Archives des maladies du cœur et des vaisseaux* [*Arch. Mal. Cœur*] **54**, 416–420, April [received June], 1961. 3 figs., 6 refs.

Rib-notching is due to hypertrophy of the intercostal arteries when they are contributing to a collateral flow, as for example in the case of coarctation of the aorta. Occasionally this sign is found in Fallot's tetralogy, developing after some years on the side on which a Blalock operation has been performed. Campbell (*Brit. Heart J.*, 1958, **20**, 253) suggested that the hypertrophied intercostal arteries are in this case helping to compensate for the loss of subclavian arterial blood flow to the arm. In the present paper, however, the authors suggest that rib-notching in Fallot's tetralogy is due to an anastomotic flow between the chest wall and the lung via vascular pleural adhesions. The sign was present in 8 patients out of a series of 320 cases of the tetralogy, an incidence of 2·5%. Pleural adhesions had formed spontaneously in 3 of these patients, 2 of whom had had pulmonary tuberculosis. In 5 cases thoracotomy had been performed, although in 2 of these the surgeon had been unable to carry out a subclavian–pulmonary artery anastomosis; nevertheless, notching developed within a few years, accompanied by some clinical improvement. In some cases the notching gradually regressed in subsequent years. *J. A. Cosh*

1179. **Long-term Results of Aortic–Pulmonary Anastomosis for Tetralogy of Fallot: an Analysis of the First 100 Cases Eleven to Thirteen Years after Operation**
M. H. Paul, R. A. Miller, and W. J. Potts. *Circulation* [*Circulation*] **23**, 525–533, April, 1961. 6 figs., 9 refs.

This report is concerned with the fate of the first 100 patients on whom Potts's operation (aorto-pulmonary anastomosis) was performed for Fallot's tetralogy at the Children's Memorial Hospital, Chicago. The authors point out that at that time (1946–8) diagnosis was not so accurate as it is to-day, and therefore the diagnosis of Fallot's tetralogy should not be regarded too rigidly. All the patients were severely incapacitated; 40 of them were under 3 years of age, 32 between 3 and 6, and 28 over 6.

Of the 100 patients, 9 died at or soon after operation —a figure which is identical with the over-all operative mortality of 9% in approximately 700 patients altogether operated on at the clinic. Ten patients died subse-

quently, 5 of them from congestive heart failure. Only 8 of the group could not be traced.

Of the 73 patients available for assessment 11 to 13 years after operation, in 7 (10%) results were classed as "excellent", in 42 (58%) as "good", in 22 (30%) as "fair", and in 2 (2%) as "poor". Cardiac catheterization was performed on 27 patients, but only in 18 was the pulmonary artery entered. Only 3 of these had grossly elevated pulmonary pressures (45, 75, and 85 mm. Hg respectively) and only 3 had an appreciably raised pulmonary vascular resistance (5·0, 15·8, and 18·0 units respectively).

The authors conclude that both the operative mortality and the poor results are closely related to the presence of too large an anastomosis leading either to left ventricular overload and congestive heart failure or to severe pulmonary hypertension or progressive pulmonary vascular obstruction. Their accepted practice now is to make the incision in aorta and pulmonary artery accurately 6·3 mm. long, which produces an anastomosis of 4 mm. diameter, except in infants, where the incisions are limited to 5 mm. *W. P. Cleland*

1180. **Cardiac Failure Due to Interatrial Communication.** (L'insuffisance cardiaque de la communication interauriculaire)
P. Broustet, G. Dubourg, H. Bricaud, G. Cabanieu, M. Dallochio, M. Trarieux, B. Ballan, and P. Coumau. *Archives des maladies du cœur et des vaisseaux* [*Arch. Mal. Cœur*] **54**, 605–620, June, 1961. Bibliography.

Atrial septal defect (A.S.D.) is generally well tolerated, but it can on occasion lead to congestive heart failure. The authors discuss a group of 14 such patients encountered among a series of 98 cases of A.S.D. which have been fully investigated at the Hôpital du Tondu, Bordeaux. The patients' ages ranged from 4 to 60 (mean 36) years. The development of congestive failure was often the climax to a period, sometimes lasting several years, of gradually diminishing exercise tolerance and as a rule had no precipitating cause. Most of the patients were in atrial fibrillation, with the usual signs of right ventricular failure, cyanosis, considerable cardiac enlargement, and dilatation of the pulmonary arteries. Heart sounds and murmurs were those usually associated with the lesion. Cardiac catheterization showed rather higher right-sided pressures in the 14 patients than in those with A.S.D. not in failure; thus the mean pulmonary arterial pressure in the former was 53 mm. Hg (compared with 32 mm. Hg in the latter), systemic blood flow was lower, pulmonary flow higher, but pulmonary arterial resistance was much the same in the two groups.

Of the 14 patients, 4 died of progressive failure and 3 following an attempt at operation. One improved on medical treatment, while 2 were much improved after surgical closure of the defect. In 6 of the 14 cases examination of the defect was possible either at operation or at necropsy; in all 6 it was of the ostia secunda type and in only 2 was it over 4 cm. in diameter. The authors conclude that ideally in patients with A.S.D. congestive failure should be prevented by corrective surgery while the patient is still fit, but if failure has already developed, surgery, in spite of its increased risks, offers the only real hope of recovery. *J. A. Cosh*

VALVULAR DISEASE

1181. **Silent Mitral Incompetence**
V. Schrire, L. Vogelpoel, M. Nellen, A. Swanepoel, and W. Beck. *American Heart Journal* [*Amer. Heart J.*] **61**, 723–732, June, 1961. 7 figs., 24 refs.

A systolic murmur, usually described as loud and holosystolic, is the conventional hallmark of mitral incompetence. Six cases of silent mitral incompetence are described in which murmurs were absent at the apex despite the presence of gross mitral regurgitation. In 3 cases, despite frequent examination over long periods, no murmurs could be heard or recorded by phonocardiography at any time. In the other 3, soft mitral systolic murmurs were sometimes present and sometimes absent. Heart failure and atrial fibrillation did not appear to be responsible for these findings.

In all 6 patients, radiologic examination showed disproportionate enlargement of the left atrium and provided the clue to the correct diagnosis. Rheumatic mitral valvular disease was proved at necropsy in one and at operation in another. Cardiac catheterization established the diagnosis but not the etiology in 2.

Gross mitral incompetence can occur in the absence of any audible systolic murmur.—[Authors' summary.]

1182. **Evaluation of the Surgical Correction of Mitral Regurgitation**
E. B. Kay, D. Mendelsohn, and H. A. Zimmerman. *Circulation* [*Circulation*] **23**, 813–822, June, 1961. 9 figs.

The authors review the results of open operation in 100 patients with varying degrees of mitral incompetence at St. Vincent Charity Hospital, Cleveland, Ohio. Of these 100 patients, 23 had pure incompetence, 34 had an element of stenosis but dominant incompetence, 29 had dominant stenosis, and 14 had destroyed valves. In the patients with pure incompetence there were either stretched or ruptured chordae tendineae. Patients with both incompetence and stenosis tended to have smaller hearts and in about a quarter of these cases the valves were calcified. All the patients with destroyed valves showed gross calcification. The exact details of the repair varied from case to case; in most cases some sort of plication of the atrioventricular ring was carried out and in many where there was tissue loss plastic material was sewn in place.

Operative deaths in the series numbered 23, but the risk varied considerably with the type of lesion. All the patients with destroyed valves died, whereas of the 23 with pure incompetence, 2 died and of the 29 with predominant stenosis, 3 died. The survivors were assessed at intervals over a period of 6 months to 3½ years after operation. The condition of 11 was considered to be "fair" and 2 had died, but in the remainder the results were good in terms of improvement in exercise tolerance

and in heart size. The electrocardiogram showed little change. In most of the patients with pure regurgitation the systolic murmur was either lessened or abolished, this change being less obvious in patients with calcified valves. There was some improvement in the majority of patients on whom catheterization was carried out after operation.

The authors conclude that the best results are achieved in the least disabled patients, and they stress the need for early rather than delayed operative treatment of mitral incompetence. *J. R. Belcher*

CORONARY DISEASE AND MYOCARDIAL INFARCTION

1183. **Clinical Experiences with Isosorbide Dinitrate (Isordil)**
J. W. Berry, R. Carney, and H. Lankford. *Angiology* [*Angiology*] **12**, 254–258, June, 1961. 1 fig., 11 refs.

The effect of a new vasodilator drug, isosorbide dinitrate ("isordil"), was investigated at St. Louis City Hospital, Missouri, in patients with angina pectoris due to ischaemic heart disease. In a dosage of 50 mg. daily it produced a marked reduction in the number of anginal attacks in 21 (87%) of 24 such patients. In comparable studies pentaerythritol tetranitrate (40 to 80 mg. daily) yielded a similar result in 20 out of 28 patients (71%), while the corresponding figure for a placebo was 2 out of 18 patients (11%). It is concluded that isordil appears to be an effective drug for the oral treatment of angina pectoris. Among various side-effects throbbing headache was the commonest, necessitating reduction of the dose in some cases and withdrawal of the drug in 4. *A. Schott*

1184. **Isosorbide Dinitrate in Angina Pectoris**
L. G. Joseph and A. Mancini. *Angiology* [*Angiology*] **12**, 264–266, June, 1961. 3 refs.

The effect of isosorbide dinitrate in a dosage of 40 mg. daily in divided doses on the number of attacks of angina pectoris due to coronary sclerosis was studied in 29 patients observed in private practice over periods varying between 25 and 100 days. Good to excellent results were obtained in 23 cases (80%), but the necessity for confirmation of this initial evaluation of the drug by means of controlled trials or "by the consensus of clinical impression" is stressed. The main side-effect was vascular headache (14 cases), but this was severe enough to necessitate discontinuation of the drug in only one case. *A. Schott*

1185. **Effects of Erythrol Tetranitrate and Amotriphene on Exercise Tolerance Tests in Angina Pectoris**
A. Ruskin. *Circulation* [*Circulation*] **23**, 681–684, May, 1961. 2 figs., 15 refs.

The author of this paper from the University of Texas Medical Branch, Galveston, describes a comparative investigation of the effects of erythrol tetranitrate and amotriphene on the response to exercise tolerance tests in angina pectoris. A group of 36 patients with angina in whom standard exercise induced changes in the electrocardiogram (ECG) were selected for the trial. All the patients had previously received glyceryl trinitrate and the investigation was designed to determine whether either of the newer drugs was more effective.

Erythrol tetranitrate was found to be effective both in reducing symptoms and in reversing the ECG changes induced by exercise. The best results were obtained with small doses initially, increased as tolerance was acquired. Amotriphene gave only limited alleviation of symptoms and reversed the ECG changes in 3 cases only. *J. Robertson Sinton*

1186. **The Concentration of Antihemophilic Globulin (AHG) in Patients with Coronary Artery Disease**
A. A. Cooperberg and J. I. Teitelbaum. *Annals of Internal Medicine* [*Ann. intern. Med.*] **54**, 899–907, May, 1961. 3 figs., 18 refs.

In a study at the Jewish General Hospital, Montreal, Canada, 12 out of 16 patients with recent or remote myocardial infarction were found to have increased thromboplastic activity in their plasma as determined by the thromboplastin generation test. Their Factor-V activity was normal, suggesting that an increased concentration of antihaemophilic globulin (A.H.G.) was responsible for the high thromboplastic activity, and this was confirmed by specific A.H.G. assay, which showed statistically significant differences between the results in 51 male patients and 29 male controls. It is suggested that the increase in A.H.G. concentration causes a hypercoagulable state of the blood and predisposes to thrombosis in patients with coronary arterial disease.

[A report of this nature must be viewed with caution, since the demonstration of an "abnormally high concentration" of a coagulation factor is always more questionable than the demonstration of a deficiency or inactivation.] *T. B. Begg*

1187. **The Effectiveness of Bilateral Ligation of the Internal Mammary Artery in Chronic Coronary Insufficiency.** (К вопросу об эффективности операции двусторонней перевязки внутренней грудной артерии при хронической коронарной недостаточности)
L. B. Šimeliovič. *Терапевтический Архив* [*Ter. Arh.*] **33**, 7–11, May, 1961. 22 refs.

Fiesca's operation was carried out on 35 patients previously treated medically with little success for their chronic angina, which in all but one (a patient with syphilitic mesoaortitis) was due to atherosclerosis of the coronary arteries. All had angina of effort, 8 also suffered from angina at rest, and 15 had a history of myocardial infarction. Hypertension was present in 11 cases, changes in the electrocardiogram (ECG) at rest in 30, extrasystoles in 5, and left bundle-branch block in one case.

During the first few days after the operation (bilateral ligation of the internal mammary arteries in the 2nd intercostal space under local anaesthesia), drug treatment being continued, the angina became more severe

in 15 patients, one developing a myocardial infarct, another paroxysmal auricular fibrillation, and a 3rd gallop rhythm with circulatory failure. In 19 of the 35 patients the blood supply of the myocardium was further diminished and in 14 of these this was confirmed by ECG findings. In spite of adequate psychological preparation tachycardia and increased blood pressure were noted in a majority of patients before and during the operation. The patients were followed for up to 2 years. Results were generally better in patients operated on during an exacerbation of the disease. In 5 cases the pain returned 14 days after the operation, in 3 in 1 to 2 months, and in 7 at a later period. In 15 cases, however, the attacks of angina disappeared or diminished in frequency. Four patients died 1 to 12 months after the operation. The results of investigation of the zones of anaesthesia seemed to indicate that the suppression or attenuation of the anginal pain in some cases was due to interruption (by the incision) of the pathway of pain sensation rather than any actual increase in the blood supply of the heart.

S. W. Waydenfeld

1188. **Serum Glutamic Oxalacetic Transaminase Activity in Acute Coronary Thrombosis with Myocardial Infarction: Relation to Prognosis**

M. McCall, A. Hertz, I. Rappaport, and W. Nelson. *American Journal of Cardiology* [*Amer. J. Cardiol.*] **7**, 673–675, May, 1961. 2 figs., 10 refs.

Serum glutamic–oxalacetic transaminase (S.G.O.T.) activity was investigated in 186 consecutive patients admitted to the Beekman-Downtown Hospital, New York, with clinical and serial electrocardiographic signs of acute myocardial infarction. Venous blood was taken within 2 hours of admission and then daily for 5 days and the S.G.O.T. activity estimated using a modification of the method of Reitman and Frankel (*Amer. J. clin. Path.*, 1957, **28**, 56; *Abstr. Wld Med.*, 1958, **23**, 154) and a colorimeter scale.

Except in those who died within 3 hours of admission, there was a significant rise in S.G.O.T. activity in all patients in the first 24 hours. Of 21 patients who died on the second and third days, 10 had levels more than 5 times normal. In these 10 cases massive infarcts were found post mortem, whereas in the other 11 only small infarcts were present. Among patients surviving after the first day with enzyme activity less than twice normal values there were no fatalities.

Thus the authors conclude that S.G.O.T. activity is a useful guide to diagnosis and immediate prognosis of acute myocardial infarction. *D. Goldman*

1189. **Oral I^{131} Triolein Tolerance Curves in Elderly Subjects with Coronary Artery Disease**

J. Edelman, H. Sandberg, E. R. Dickstein, and S. Bellet. *American Journal of Cardiology* [*Amer. J. Cardiol.*] **7**, 676–680, May, 1961. 3 figs., 20 refs.

Recent studies have demonstrated that middle-aged subjects with myocardial infarction metabolize orally administered ^{131}I triolein in an abnormal manner. The authors of this paper therefore decided to study ^{131}I tolerance curves in elderly patients with clinical and electrocardiographic evidence of coronary artery disease at the Philadelphia (Pennsylvania) General Hospital. Of the 26 patients selected for study, 10 were 60 or more years old. Each received a test meal consisting of ^{131}I triolein, ginger ale, and milk after an overnight fast, having for the previous 2 days been given 20 drops of Lugol's solution daily. Oxalated blood samples were taken at regular intervals during the subsequent 24 hours and their radioactivity estimated.

Increased radioactivity was found in the whole blood and circulating lipoprotein fraction in all patients under 60, but in the older groups the levels were similar to those of normal controls. When ^{131}I triolein was administered intravenously to patients with coronary arterial disease the rate of decline of radioactivity was equal to that found in controls.

The authors suggest that the younger patients have increased absorption or deficient utilization of the lipid. Similar results have been reported for diabetic patients under 60. *D. Goldman*

1190. **Aetiology of Coronary Heart Disease in Old Men**

R. M. Acheson. *British Journal of Preventive and Social Medicine* [*Brit. J. prev. soc. Med.*] **15**, 49–60, April, 1961. Bibliography.

Of a random sample of 267 pensioners, aged 65 to 85 years, of a commercial firm in Dublin, 221 were interviewed and examined physically between January, 1957, and June, 1958.

In addition to a clinical examination of the heart and lungs, the ECG was recorded at rest and when possible, after exercise; height, weight, and certain other body measurements, and blood pressure were recorded, the urine was examined, and information was obtained about habits and past illnesses. On the basis of a history of angina pectoris and/or ECG changes, 88 men (40%) were diagnosed as having coronary heart disease; of the 58 men who performed an exercise tolerance test satisfactorily, 22 had a normal ECG immediately afterwards, and since they gave no history of angina pectoris were classified as "healthy". When all the 88 men with coronary heart disease were compared with the remaining 133 men they were found to be significantly older ($P<0.05$), to have a higher diastolic blood pressure ($P<0.05$), and to have a lower ponderal index—that is, they were physically stockier ($P<0.001$). The two groups did not differ significantly in respect of total serum cholesterol, $\beta:\alpha$ lipoprotein ratio, frequency of pre-β-lipoprotein, subcutaneous fat, use of tobacco, alcohol consumption, or physical activity at work. However, 8 of the 88 cases in the coronary group had ECG evidence of myocardial infarction, and in them the serum cholesterol was significantly higher than in the controls ($P<0.05$). These results are compared with those of other authors and it is concluded that coronary heart disease in old men is due principally to atherosclerosis rather than to thrombosis of the major vessels, and that its aetiology differs from that of the acute thrombotic episodes which are becoming increasingly common in middle-aged men.—[From the author's summary.]

1191. **C-Reactive Protein and Blood Fibrinogen in Myocardial Infarction.** (С-реактивный белок и фибриноген крови у больных инфарктом миокарда)
G. A. Raevskaja. *Советская Медицина* [*Sovetsk. Med.*] **25**, 16–22, April, 1961. 21 refs.

The serum C-reactive protein level was determined in 52 patients with myocardial infarction and in 44 with angina pectoris by the method of Anderson and McCarthy. The reaction was considered to be negative in the absence of precipitate and assessed as a trace, weakly positive, positive, and strongly positive respectively if the precipitate was less than 1 mm., between 1 and 2 mm., 2 to 3 mm., and 4 mm. or over respectively. Of the patients with myocardial infarction, 37 were men and 15 women, all aged between 45 and 60 years. The condition was serious in 18 patients, of whom 5 died. In 24 of the patients with myocardial infarction estimations were performed on the first and 5th days and then every 2 to 4 days until it became negative.

In all patients investigated before the 15th day the reaction was positive, in some cases as early as the first day. After the 15th day it had already become negative in milder cases. Of the 18 seriously ill patients, the reaction was strongly positive in 16 and positive in 2. In milder cases the reaction remained positive for 12 to 30 days and in more severe cases for up to 50 days; in general it remained positive for longer periods in the presence of complications. In all 44 patients with angina the reaction was negative.

The blood fibrinogen content was then determined by means of Bang's modification of Gramm's method in 58 patients with myocardial infarction. The values for 15 healthy controls ranged from 0·3 to 0·6 g. per 100 ml. In 5 of the patients the value remained normal throughout, but in the remainder an increase was observed from the first day, reaching a maximum (1·0 to 1·9 g. per 100 ml.) between the 5th and 15th days and returning to normal over a period of up to 45 days. As in the case of C-reactive protein there was a definite correlation between the extent of rise in level and the severity of the condition. The blood fibrinogen content was slightly raised or near the upper limit of normal in most of the patients with angina pectoris.

The C-reactive protein value was also estimated in 200 patients with various conditions; the protein was found to be present in pneumonia, pneumosclerosis, pleurisy, active rheumatic disease, other cardiac diseases with heart failure, nephritis, tumours, and rheumatoid arthritis. *S. W. Waydenfeld*

1192. **Serum Lactic Dehydrogenase Estimations in Myocardial Infarction**
T. W. Stewart and F. G. Warburton. *British Heart Journal* [*Brit. Heart J.*] **23**, 236–242, May, 1961. 15 refs.

A comparison of results obtained in 20 cases of myocardial infarction has been made [at Hope Hospital, Salford], employing serum glutamic oxalacetic–transaminase (S.G.O–T.) and serum lactic dehydrogenase (S.L.D.) estimations. The findings show that the results of American workers have been confirmed, and that S.L.D. estimation allows of greater latitude in sampling, due to its longer period of elevation. Its estimation by the method of the Sigma Co., using Sigma reagents, is satisfactory for the purpose. Although it is raised in other conditions, it is doubtful if this represents a drawback to its use by discriminating workers as a test for myocardial infarction, as these other conditions are mostly clinically distinct from myocardial infarction. In doubtful cases, where the S.L.D. is not greatly elevated, one or two serial tests will usually resolve the difficulty, as the levels tend to remain static in conditions other than myocardial infarction over the short period of time involved, instead of following the typical course of rise and fall. The explanation of this would appear to be that in myocardial infarction the enzyme is liberated from damaged cells, causing the serum enzyme activity to reach a peak, usually about 3 to 4 days after infarction, and then slowly to return to normal. Other conditions have raised S.L.D. activity, due to reasons explained but the serum level remains steady over the period involved, and is not usually so greatly raised.—[Authors' summary.]

1193. **Prognosis of the Men Returning to Work after First Myocardial Infarction**
G. E. Dimond. *Circulation* [*Circulation*] **23**, 881–885, June, 1961. 7 refs.

The prognosis after an initial myocardial infarction was studied in 202 male operating employees of the New York Central Railroad who returned to full-time work after the first attack of infarction. The subjects were highly selected; before infarction they had undergone pre-employment and periodical medical examinations which had largely eliminated diabetes, severe hypertension, and gross obesity as significant factors. Subjects with valvular heart disease were also excluded.

It was found that the prognosis in men able to return to work was better than in those retiring from work, this being due in part to a "lesser incidence of myocardial failure and a better ability to survive a second infarction". The 5-year survival rate was 83% and the 10-year 57%. The author states that 25% of the patients were dead or were totally disabled at the end of 8 years and 50% at the end of 10 years, death or disability being largely due to recurrent myocardial infarction. *R. Wyburn-Mason*

BLOOD VESSELS

1194. **Serum Cholesterol and Atherosclerosis in Man**
K. S. Mathur, N. L. Patney, V. Kumar, and R. D. Sharma. *Circulation* [*Circulation*] **23**, 847–852, June, 1961. 1 fig., 21 refs.

The correlation between a raised serum cholesterol level and clinically diagnosed atherosclerosis has been repeatedly demonstrated. In the present study the authors chose a more critical method than clinical diagnosis, comparing the degree of atherosclerosis seen at necropsy with the post-mortem blood cholesterol level. A preliminary study in which blood was collected before and after death in 20 unselected patients showed that the cholesterol level after death did not differ significantly

from that in life provided the blood was collected within 16 hours of death. An " atherosclerotic index " was then worked out for each of 200 subjects coming to medico-legal necropsy on the basis of the degree of atherosclerosis found in the aorta and coronary and cerebral arteries.

A statistically significant correlation was found in this series between the cholesterol levels and age of the subject up to the fifth decade, thus confirming the work of previous authors. When the cases were divided according to the severity of the atherosclerosis a rise in the mean serum cholesterol level was found in the first 6 successive groups of aortic atherosclerosis. However, when the patient's age was excluded from the correlation only a statistically insignificant interrelationship could be observed between serum cholesterol levels and severity of atherosclerosis. The authors therefore conclude that no definite correlation can be established between the serum cholesterol level and the degree of severity of atherosclerosis in the arteries examined.

Z. A. Leitner

1195. **Fibrinolysin Therapy in Thromboembolic Disease** W. A. Randolph and H. M. Starling. *Angiology* [*Angiology*] **12**, 179–194, May, 1961. 21 refs.

This paper describes the use of the fibrinolytic agent " actase " in the management of 23 patients with a variety of thromboembolic incidents, including superficial and deep vein thrombosis, pulmonary embolism, and intra-arterial occlusion, at the City Memorial Hospital, Winston-Salem, North Carolina. The preparation used was made from the plasminogen in the euglobulin fraction of human plasma by streptokinase activation. The patients received from one to 17 intravascular infusions in doses of 50,000 to 150,000 ortho fibrinolytic units reconstituted in 20 to 250 ml. of 5% dextrose in water or normal saline. An ortho fibrinolytic unit is described as " that amount of a standard preparation required to alter the turbidity of a standard fibrin clot 50% in 10 minutes ".

Because of the proteolysis of plasma coagulation factors and the presence of fibrinogen breakdown products abnormal haemorrhage is an expected side-effect of thrombolytic therapy. In the present series of cases there was no such evidence of bleeding, however, but a prolongation of the one-stage prothrombin time was occasionally reported. There was a reduction in leucocyte count in all 6 patients with leucocytosis on admission, but no change was noted in patients with a normal count. Subcutaneous extravasation of the infused fluid had only the same effect as that produced by saline or dextrose solutions. No allergic skin responses were seen. Transient hypotension occurred in 2 female patients with thrombophlebitis. The infusions did not appear to affect the temperature course, and in only one case did the temperature rise more than 1·8° F. (1·0° C.). A few patients had gastro-intestinal symptoms after the infusions. At no time during the course of treatment of venous thrombosis did pulmonary emboli develop, and none of the patients presenting with an initial episode of acute thrombophlebitis developed a post-phlebitic syndrome.

A. S. Douglas

SYSTEMIC CIRCULATORY DISORDERS

1196. **Tropafen in the Treatment of Hypertensive Disease.** (Лечение гипертонической болезни тропафеном)

C. A. Levina and A. I. Romanovskaja. *Советская Медицина* [*Sovetsk. Med.*] **25**, 67–70, April, 1961.

" Tropafen " is a recently synthesized Soviet preparation with marked adrenolytic, slight cholinolytic, and direct vasodilator activity. It has been shown to exert a marked and prolonged hypotensive effect both in healthy animals and in those with experimental renal hypertension. Its toxicity is low.

In a clinical trial 41 patients (24 men and 17 women), most of whom had hypertensive disease of Grade II and all of whom had been treated previously with little success, were given tropafen once or twice a day for 10 to 20 days by intramuscular injection, the dosage being 0·5 to 2 ml. of a 2% solution depending on the response. The hypotensive effect of the drug was observed 15 minutes after the injection, reached its maximum in about 30 to 45 minutes, and disappeared after 1 hour. The systolic blood pressure was reduced in a majority of the patients from between 180 and 230 before to between 121 and 180 mm. Hg after treatment, while the diastolic pressure fell from between 91 and 150 to 80 to 90 mm. Hg. The temporal arterial systolic pressure fell from a mean of 100 to 90 mm. Hg. The oscillographic index was determined in 15 patients. Before and after treatment it remained between 2 and 10 mm. and in only 4 cases reached 11 to 20 mm. Side-effects, such as increased headache, giddiness, and general weakness, were observed during the first few days of treatment in 4 patients; in only one, however, had the treatment to be discontinued, the side-effects disappearing in the others. The results were assessed as good in 27 and satisfactory in 11 of the 41 cases. The effect following a course of treatment lasted only 2 or 3 days, but subjective improvement persisted for 2 to 3 weeks. The results were best in patients with cerebral and cerebro-cardiac forms of the disease.

S. W. Waydenfeld

1197. **Relationship between Arterial Pressure and Exertional Angina Pectoris in Hypertensive Patients**

A. J. Georgopoulos, F. M. Sones Jr., and I. H. Page. *Circulation* [*Circulation*] **23**, 892–900, June, 1961. 5 figs., 11 refs.

Some workers have observed raised arterial blood pressure during attacks of angina pectoris and others have reported relief of exertion angina in hypertensive patients by satisfactory control of hypertension. Further, angina may occur in hypertensive patients during lowering of arterial pressure. At the Cleveland Clinic Hospital, Cleveland, Ohio, an investigation was carried out to determine the possible relationship between arterial pressure and exertional angina pectoris in 7 hypertensive patients, 5 with and 2 without coronary arterial disease as determined by Sones's technique. Radiological as well as electrocardiographic (ECG) evidence of left ventricular hypertrophy was present in all patients. None had a history or ECG evidence of

recent or remote myocardial infarction. The 5 patients with coronary arterial disease had not received any hypotensive drugs and had moderate or severe hypertension. The 2 patients with normal coronary arteries had been treated with guanethidine and had normal supine arterial pressure and significant postural hypotension. All the patients were subjected to exercise in the sitting and supine positions. In the 5 patients with coronary arterial disease there was a striking arterial pressure elevation during exercise in both positions, followed by angina and ECG changes; when the pressor response to exercise was eliminated by intravenous administration of sodium nitroprusside these effects were not observed. In the 2 patients with normal coronary arteries who had orthostatic and exertional hypotension, exercise in the sitting position resulted in intense hypotension followed by angina and ECG changes. In the supine position exercise caused only minimal pressure changes and no angina. It is concluded that in the former group of patients further increase in arterial pressure during exercise is an important factor in precipitating angina. In the latter group lowering of the arterial pressure during exercise is a factor, probably by reduction of coronary artery perfusion pressure.

R. Wyburn-Mason

1198. **Electrolyte Excretion and Hypotensive Response**
N. Fallis and R. V. Ford. *Journal of the American Medical Association* [*J. Amer. med. Ass.*] **176**, 581–584, May 20, 1961. 5 figs., 6 refs.

Potassium depletion is often a problem in patients receiving long-continued treatment with thiazide diuretics. In this study, reported from Baylor University College of Medicine, Houston, Texas, the authors have investigated the influence of different dietary intakes of sodium and potassium on electrolyte balance and the response of the blood pressure to hydrochlorothiazide in 5 patients with hypertensive cardiovascular disease. The three regimens tested were as follows. Diet 1 contained 50 mEq. of sodium and 50 mEq. of potassium daily and was continued for 22 days, hydrochlorothiazide being given first in a dose of 50 mg. daily for 7 days followed by 100 mg. daily for 7 days. (2) A similar procedure was repeated with Diet 2, which contained 100 mEq. of sodium and 50 mEq. of potassium daily. (3) In the final study period (11 days) the patients were given Diet 3, which contained 50 mEq. of sodium and 100 mEq. of potassium daily, together with 100 mg. of hydrochlorothiazide daily for the last 7 days.

During administration of Diet 1 the mean systolic blood pressure fell from 127 to 110 mm. Hg with 50 mg. of hydrochlorothiazide daily and from 132 to 108 mm. Hg with 100 mg. daily. The higher dose of the diuretic caused more potassium depletion (cumulative negative balance −86 mEq. as against +3 mEq.), but very little more sodium depletion or greater fall in blood pressure. On Diet 2 the mean blood pressure fell from 132 to 128 mm. Hg with 50 mg. of hydrochlorothiazide daily, but from 132 to 112 mm. Hg with 100 mg. daily. The higher dose of diuretic caused significant potassium depletion, the cumulative potassium balances now being −30 and −80 mEq. respectively. Diet 3 together with 100 mg. of hydrochlorothiazide daily brought about a fall in mean blood pressure from 127 to 109 mm. Hg and no potassium depletion. The authors conclude that the most favourable regimen for a hypertensive patient consists of 50 mg. of hydrochlorothiazide daily, moderate salt restriction (3 g. of sodium chloride per day), and a potassium-enriched diet.

[The results of electrolyte balance studies are fully reported, but more details of the blood pressure measurements would have been welcome. It is stated that the blood pressure was measured daily, but no data on individual variations are given. It is clear from the mean blood pressure values quoted that the hypertension was of only mild degree before treatment.]

C. T. Dollery

1199. **The Serum Cholesterol and Lecithin Concentrations and Their Correlation in Patients with Primary Arterial Hypotension.** (Содержание холестерина и лецитина и их соотношение у лиц с первичной артериальной гипотонией)
M. B. Rafalovič. *Клиническая Медицина* [*Klin. Med.* (*Mosk.*)] **39**, 116–119, June, 1961. 33 refs.

The author notes that the number of cases of hypotension has progressively increased since the end of the last war. According to different authorities primary arterial hypotension occurs in from 2·5 to 12·5% of all adults. The main symptoms, apart from the low blood pressure, are headaches, vertigo, increased physical and mental fatigue, general debility, irritability, and emotional exhaustion. In 1946 Lang suggested that the hypotension was due to a neurosis of the higher vascular motor centres. It has been shown experimentally that lecithin has the ability to maintain the cholesterol of the plasma in a colloidal-soluble state, thus preventing its sedimentation and infiltration into the layers of the vessels. In atherosclerosis, especially in sclerosis of the coronary vessels, the blood lecithin level is very much lowered and, a fact especially important, the lecithin:cholesterol ratio is reduced.

In the present study 90 patients with primary hypotension, that is, a blood pressure of between 95/55 and 80/50 mm. Hg, were investigated, all patients with chronic infections and intoxications being excluded. In regard to age, 9 of the patients were aged between 20 and 29 years, 52 between 30 and 39, and 17 between 40 and 49. Taking the normal value for blood cholesterol to lie between 160 and 230 mg. per 100 ml. and that for lecithin as 125 to 250 mg. per 100 ml. it was found that the serum lecithin level in most of the patients was definitely increased, being below 200 mg. per 100 ml. in only 7 and above 250 mg. per 100 ml. in 34 of the 90 patients. The lecithin:cholesterol ratio (normally between 0·7 and 1·7) also showed a definite increase in these hypotonic patients; thus in only 3 cases was the ratio lower than 1 (0·8 to 0·99), in 50% it was about 1·3, and in 9 cases it varied from 1·7 to 1·99.

It is concluded that the occurrence in patients with primary arterial hypotension of a high blood lecithin level and a high lecithin:cholesterol ratio indicates, to a certain degree, that they are unlikely to develop atherosclerosis.

H. W. Swann

Clinical Haematology

1200. **Bone Marrow Transplantation in Certain Hypoplastic Blood Diseases.** (О пересадках костного мозга при некоторых гипопластических состояниях системы крови)
V. A. Almazov, S. I. Rjabov, and M. M. Tušinskaja. *Терапевтический Архив* [*Ter. Arh.*] **33**, 89–94, May, 1961. 3 figs., 5 refs.

The authors report the results obtained in 3 patients with panmyelophthisis and 2 with agranulocytosis who were treated with intraosseous transplantations (into the sternum or ilium) of fresh bone marrow taken from donors of the same blood group. In order to prevent the development of immunological reactions the same individual donor was used for each patient even if more than one transplant was required; also the injections were preceded and followed by administration of ACTH and prednisone. To one of the 2 patients with agranulocytosis 3 injections each of 10 ml. of marrow were given at 2 days' intervals and the blood picture returned to normal in 3 weeks; in the other, who received one injection of 20 ml., the blood picture became normal in 18 days. Both patients remained well. A third patient with pancytopenia and a haemoglobin value of 14% was given 4 injections (a total of 80 ml. of marrow) with improvement in the blood picture after 3 months; 10 months later this patient was well and able to carry out housework, the blood picture being normal. The 4th patient, who had panmyelophthisis and was admitted *in extremis*, was given 12 ml. of bone marrow but died 14 hours later. [The fifth patient is not further mentioned.]
S. W. Waydenfeld

1201. **Pernicious Anaemia and Gastric Cancer in England and Wales**
R. W. Payne. *British Medical Journal* [*Brit. med. J.*] **1**, 1807–1809, June 24, 1961. 5 figs., 18 refs.

In this communication from St. Thomas's Hospital, London, the author reports a study of the geographical variation in the mortality from cancer of the stomach and pernicious anaemia in England and Wales. Figures of population and the number of deaths ascribed to pernicious anaemia and subacute combined degeneration of the spinal cord and to malignant neoplasms of the stomach were obtained from the Registrar-General for the 5 years 1954–8. These figures were divided into sex and age groups for each of the Registrar-General's 10 standard regions. Mortality rates for pernicious anaemia and gastric cancer were calculated for each age group of each sex for the whole country. From this the expected number of deaths for each of the two groups in the 10 regions was determined, assuming a uniform mortality rate over the country. The ratio of the expected number of deaths to the actual number that occurred in each of the regions was then expressed as a percentage; this gave the comparative mortality figure.

The comparative mortality figures for pernicious anaemia were found to be highest in areas in the north and west and lowest in the south and east of the country. This was also found to be true for gastric cancer, with a marked positive correlation with the comparative mortality figures for pernicious anaemia statistically.

It is suggested that the apparent correlation between pernicious anaemia and gastric cancer may imply a common aetiology. There are, for example, marked familial tendencies in both diseases. The more frequent occurrence of blood group A in the two groups would not explain the geographical variation in incidence, as blood group A is more common in the south and east. Geological factors that have been noted are the association of gastric cancer with areas of underlying igneous rock and soil with high moisture content and high organic carbon and biological activity and areas which are watered by streams with high natural radioactivity. Similarly it has been noted that there is a high incidence of fatal pernicious anaemia in those areas where the soil is deficient in cobalt.

The author concludes that the role of trace elements and similar aetiological factors in these two diseases warrants further study. *J. S. Malpas*

NEOPLASTIC DISEASES

1202. **The Question of Increased Haemolysis in the Pathogenesis of Anaemia in Malignant Lymphogranuloma.** (Zur Frage der gesteigerten Hämolyse in der Pathogenese der Anämie beim bösartigen Lymphogranulom)
V. Brabec, J. Brousil, B. Friedmann, and V. Šebestík. *Folia haematologica* [*Folia haemat. (Lpz.)*] **78**, 17–28, 1961. 2 figs., 22 refs.

Working at the Institute for Haematology and Blood Transfusion, Prague, the authors have attempted to assess the role played by the shortening of the life span of erythrocytes in the pathogenesis of the secondary haemolytic anaemia which usually accompanies malignant lymphogranuloma, and also the influence of intracorpuscular and extracorpuscular factors in the destruction of erythrocytes.

The total of 25 cases studied were divided according to the severity of the disease into three stages: (1) 3 patients with only a few affected lymph nodes and no general symptoms; (2) 13 with two or more groups of affected lymph nodes, a subfebrile temperature, and an increased erythrocyte sedimentation rate (E.S.R.); and (3) 9 with generalized lymphogranulomatous nodes in the abdominal viscera, bones, and lungs, together with high fever, a high E.S.R., profuse perspiration, leucocytosis, and anaemia. The degree of haemolysis, assessed on the basis of the life span of erythrocytes, was estimated by Mollison's modification of the differential agglutina-

tion method of Ashby and also by labelling the cells with radioactive chromium (^{51}Cr), the results being expressed in terms of half-life values. When the ^{51}Cr values were corrected by the method of Read *et al.* (*Amer. J. med. Sci.*, 1945, **220**, 40) the results by the two methods were closely similar (normal 45 to 65 days).

In all 3 patients in Stage 1, 6 in Stage 2, and one in Stage 3, the erythrocyte life span was normal, as was the number of erythrocytes, but in 7 the haemoglobin level was decreased. In 9 patients (8 in Stage 2) the life span was shortened (14 to 35 days), in 4 the erythrocyte count was decreased, and the majority showed a low haemoglobin level. In the remaining 7 patients, all in Stage 2 and all showing hepatosplenomegaly and slight reticulocytosis, the half-life values were greatly reduced (10 to 25 days). The result of the direct Coombs test was negative in all cases and autohaemolysis was present in only one-third of the patients. In no case did the site of destruction of the erythrocytes differ significantly as between the liver and spleen.

The authors conclude that while hyperhaemolysis is less characteristic of malignant lymphogranuloma than of leukaemia, it nevertheless plays a part the importance of which varies with the stage of the disease, but it is not entirely responsible for the anaemia. It is suggested that the haemolysis is probably due to extracorpuscular factors which are not at present completely understood.

Ethel Browning

1203. **The Mechanism of the Development of Anemia in Untreated Chronic Lymphatic Leukemia**
P. Wasi and M. Block. *Blood* [*Blood*] **17**, 597–609, May, 1961. 8 figs., 34 refs.

The mechanism of the development of anaemia has been studied at the University of Colorado Medical Center, Denver, in 20 patients with untreated chronic lymphatic leukaemia, in 15 of whom the disease was accidentally discovered when determining leucocyte counts for symptoms unrelated to leukaemia. Bone-marrow specimens were obtained and sections prepared for estimation of the relative amount of fat, myeloid (erythropoietic and leucopoietic), and lymphatic tissue. Erythrocyte survival times were also determined with the use of radioactive chromium. The patients were divided into two groups: in Group I were 14 patients with a haemoglobin level above 14 g. per 100 ml., and in Group II 6 patients with a level below 12·7 g. per 100 ml. It is pointed out that in normal individuals the amount of myeloid tissue in the marrow varies from 20 to 40%, the remainder being fat, and only one or two small lymphatic nodules are seen. In the patients in Group I an increased amount of lymphatic tissue composed of small foci of small lymphocytes was always found in the marrow, and in some patients large nodules of lymphatic tissue were seen. Except for one case, the amount of myeloid tissue was in the normal range and any increase in lymphatic tissue was at the expense of the fat. In Group II there was a marked replacement of myeloid tissue and fat by lymphatic tissue, so that the marrow consisted primarily of sheets of lymphocytes with only rare myeloid cells. The erythrocyte survival rates were mainly within the normal range, only 3 of the 14 patients in Group I having a slightly reduced survival time and only one in Group II a marked reduction in erythrocyte half-life.

The authors discuss the findings and attempt to relate them to the pathogenesis of anaemia in chronic lymphatic leukaemia. It would appear that there are several stages in the development of anaemia in chronic lymphatic leukaemia. At first there is no anaemia because there is a normal amount of erythroblastic tissue capable of producing erythrocytes. In the next stage the bone marrow is extensively infiltrated with lymphatic tissue, the amount of erythroblastic tissue is less than normal, and the patients are mildly anaemic owing to a decrease in erythrocyte formation, the rate of erythrocyte destruction remaining normal. In the most advanced stage the fat and erythroblastic tissue are almost completely replaced by lymphoid tissue, so that production of erythrocytes is greatly reduced and the anaemia is aggravated by increased erythrocyte destruction.

R. F. Jennison

1204. **Circulating Antibodies in Reticuloses**
M. Barr and G. H. Fairley. *Lancet* [*Lancet*] **1**, 1305–1310, June 17, 1961. 6 figs., bibliography.

Previous reports on the formation of circulating antibodies in patients with malignant diseases of lymphoreticular tissue have been conflicting. The formation of tetanus antitoxin in response to primary immunization with tetanus toxoid was therefore studied at St. Bartholomew's Hospital, London, in 21 patients with chronic lymphatic leukaemia and lymphosarcoma and in 21 with other forms of reticulosis. A significantly impaired response was obtained in 18 of the first group and in 13 of the second. Failure to produce antitoxin was unrelated to the duration, severity, or extent of the disease or to age or therapy, but was correlated to some extent with an abnormal serum γ-globulin level, whether this was elevated or depressed.

The formation of antibodies on reimmunization was then assessed by measuring the tetanus antitoxin response in 15 patients who had been immunized with tetanus toxoid in the past, as was also the formation of anti-A isoagglutinins and α-haemolysin in 31 patients, it being assumed that the response to blood group-A substance present in tetanus toxoid was a secondary one as it was considered virtually certain that all these patients had been in contact with this widely distributed substance at some time in the past. It was found that in these reimmunized patients who were suffering from malignant diseases of the lymphocytes the production of antibody was also grossly impaired and that, as with the primarily immunized group, the response was not related to duration, severity, or extent of the disease, age, or therapy. In patients suffering from other reticuloses, however, the response was normal or only slightly impaired.

It is concluded that impaired antibody production is an integral part of these diseases, occurring most commonly in malignant diseases of the lymphocytes, and that the conflicting reports mentioned above regarding antibody production may in part have been due to failure to distinguish between primary immunization and reimmunization.

J. L. Markson

Respiratory System

1205. **Degeneration of the Ciliated Cells of the Bronchial Epithelium (Ciliocytophthoria) in Its Relation to Pulmonary Disease**

G. N. PAPANICOLAOU, E. L. BRIDGES, and C. BAILEY. *American Review of Respiratory Diseases* [*Amer. Rev. resp. Dis.*] **83**, 641–659, May, 1961. 42 figs., 17 refs.

Ciliocytophthoria is defined as the phenomenon of mass degeneration of the ciliated components of the bronchial epithelium occurring in certain cases of acute and chronic pulmonary disease, which can be detected by microscopical study of the sputum.

Observations have been made (at Cornell University Medical College, New York) on sputum smears and several varieties of ciliocytophthoria recognized. These could be classed into three general groups: (*a*) changes affecting the nucleus; (*b*) changes affecting the cytoplasm; and (*c*) fragmentation and disintegration of the ciliated cell. Smears obtained from 1,000 patients were examined; 500 of these were from essentially healthy subjects who reported at the Strang Prevention Clinic for routine examination and 500 were chiefly from patients with obscure clinical symptoms involving a suspicion of lung cancer.

Evidence of ciliated epithelial degeneration was thus obtained and correlated with the clinical condition of the subjects. Many of the otherwise normal subjects were suffering from mild viral respiratory infections and others later acquired influenza during the 1957 epidemic. There was a far greater degree of ciliocytophthoria in those with a virus infection than in healthy subjects. Some otherwise healthy subjects who developed a virus infection during the subsequent 3 months showed excessive ciliocytophthoria in their sputum smears. These subjects were possibly harbouring a latent respiratory virus infection at the time. It is estimated that in some cases there was a loss of over half a million cells in one day. Such a loss must result in the formation of non-ciliated areas on the bronchial mucosa, opening the gateway to the action of extraneous carcinogens and other injurious agents.

The patients in the second group were for the most part of an older age and the majority were in hospital with acute bronchitis or bacterial pneumonia. It was more difficult to correlate ciliocytophthoria with the development of bronchial carcinoma, since many of the malignant cases were complicated by an associated inflammatory condition. However, the presence of metaplastic cells in smears strongly positive for ciliocytophthoria has been repeatedly observed.

A case is described in which positive ciliocytophthoria findings were followed by the appearance first of metaplastic cells and then malignant cells. A subsequent operation revealed the existence of an early epidermoid carcinoma of the lung. *G. Clayton*

1206. **Primary Lung Abscess: Analysis of Therapy and Results in 55 Cases**

W. R. FIFER, K. HUSEBYE, C. CHEDISTER, and M. MILLER. *Archives of Internal Medicine* [*Arch. intern. Med.*] **107**, 668–680, May, 1961. 7 figs., 24 refs.

In this paper from the University of Minnesota, Minneapolis, the authors review 55 consecutive cases of primary lung abscess collected between 1952 and 1956 at 4 large metropolitan teaching hospitals. Adequate medical therapy was tried in 51 cases, the other 4 patients being treated surgically before adequate conservative treatment had been given, but only in 28 of the 51 were the results successful according to the criteria laid down. Failure occurred most often in older patients and diabetics and was favoured by chronicity or delay. The larger the abscess, the less likely was it to heal, but site did not appear to be significant. Bronchostenosis occurred exclusively in the "failure" group, but lesser bronchial inflammatory changes occurred equally in both groups. Gram-negative bacilli were found in 23 patients, pathogenic staphylococci in 18, and pneumococci and streptococci in 8 each. The authors state that the combination of Gram-negative bacilli and coagulase-positive staphylococci in the same patient was associated with treatment failure in 5 out of 7 cases.

The average duration of antibiotic therapy was 47 days, and 191 courses were given to the 55 patients. Intravenous penicillin, 1,000,000 units 12-hourly, was given to 32 patients, in 21 of whom the treatment was successful. Of the 19 patients treated medically who did not receive this therapy, success was attained in 7 only. Analysis of the antibiotic treatment revealed inadequate treatment in 11 of the 22 failures. A further 5 failures were due to combined resistance, which made treatment impossible.

Surgical treatment in 16 cases included primary external drainage in 5 with unsatisfactory results. Four patients underwent segmental resection and 7 lobectomy; one died and another required further operation for a bronchopleural fistula, but in the others the operation was successful. Spontaneous closure of abscess cavities, long after cessation of treatment, occurred in 12 of 19 patients who were discharged with a persistent cavity, but whose condition was otherwise clinically satisfactory. *B. Golberg*

1207. **The Occurrence of Azotemia in Pneumococcal Pneumonia**

J. P. SANFORD and J. A. BELLI. *American Review of Respiratory Diseases* [*Amer. Rev. resp. Dis.*] **83**, 704–710, May, 1961. 1 fig., 29 refs.

This study is reported from the University of Texas Southwestern Medical School, Dallas, "to re-emphasize the frequent occurrence of azotemia during the course

of otherwise uncomplicated treated pneumococcal pneumonia and also to characterize the clinical features of such patients".

For this purpose the records of 44 patients with a bacteriologically confirmed diagnosis of pneumococcal pneumonia were reviewed. A blood urea nitrogen level of 25 mg. per 100 ml. was taken as the upper limit of normal, and 21 patients had concentrations in excess of this figure. There was no correlation with age and sex or with the duration of the illness before hospital admission, nor was there any correlation between azotaemia and other manifestations of overwhelming infection. There was a history of renal disease and raised blood urea level in 3 patients; they all had an increase in the degree of azotaemia and 2 died.

Some degree of hypochloraemia is common in pneumococcal pneumonia, but values below 90 mEq. per litre occurred only in patients with associated azotaemia. The azotaemia is primarily the result of an increased nitrogen load delivered to the kidneys. The glomerular filtration rate does not seem to be severely reduced; in 3 out of 4 patients the serum creatinine level was normal. Three patients died, and all showed rapid increase in azotaemia with an associated hyperkalaemia. Included in this figure are the 2 patients already mentioned as having pre-existing renal disease.

The records of another group of 24 patients with a clinical diagnosis of pneumococcal pneumonia but no bacteriological confirmation were also studied. The findings were comparable with those in the group with bacteriologically confirmed disease. On the other hand in a group of 12 adult patients with pneumococcal meningitis not one had a blood urea nitrogen concentration in excess of 25 mg. per 100 ml.

It is concluded that azotaemia is not a grave prognostic finding unless pneumococcal pneumonia occurs in patients with coexistent renal disease.

G. Clayton

1208. **Therapeutic Action of Tetracycline–Oleandomycin Combination in Severe Infections of the Respiratory Tract**
C. M. VILLAFANE and A. C. FORTE. *International Record of Medicine* [*Int. Rec. Med.*] **174**, 88–93, Feb. [received April], 1961. 12 refs.

At the Chest Clinic, Rosario, Argentine, 41 patients suffering from a variety of severe acute respiratory infections, including apical abscess (3 patients) and empyema (14), were treated with a combination of tetracycline and oleandomycin ("sigmamycin"). Of the 41 patients, 9 were under one year old. Where necessary, other treatment was carried out—for example, drainage of empyema.

Satisfactory results were obtained in all except 2 patients with cor pulmonale, in whom moniliasis later developed. Mild diarrhoea was observed in a few cases. Sensitivity tests showed that the antibiotic combination was "more active than the two components alone or their sum and that it could be effective despite resistance to one or both components". The combination was very effective in curing staphylococcal infections.

Bernard J. Freedman

1209. **Observations on the Natural History of Bronchioloalveolar Carcinoma: Experience with Twenty-one Cases**
J. W. BELL and K. P. KNUDTSON. *American Review of Respiratory Diseases* [*Amer. Rev. resp. Dis.*] **83**, 660–667, May, 1961. 4 figs., 14 refs.

During an 8-year period 21 cases of bronchioloalveolar carcinoma were seen at the Veterans Administration Hospital, Seattle, Washington. Experience from these cases is presented with regard to clinical detection and factors influencing the length of survival. An attempt is made to relate the survival period to the distribution and duration of disease and to evaluate the results of surgery.

The age of the patients varied from 34 to 77 years, with a mean age of 57·7 years. Ten presented themselves with widespread pulmonary symptoms; 6 of these had neurological complaints, and in 4 the pulmonary shadow had been picked up on a routine x-ray survey as a discrete "coin" lesion. There were various other x-ray findings, but commonly the appearances were those of a rather ill-defined segmental or lobar pneumonia. Almost every patient had had a normal chest radiograph 6 months to 2 years before detection of the abnormal shadow. Other investigations included bronchoscopy, scalene-node biopsy, sputum cytology, and lung biopsy.

Post-mortem examination was performed on 17 of the patients, all but 2 of the deaths being the result of carcinoma. There was evidence of extrathoracic metastasis in 12 patients—to the abdominal viscera in 7 and to the central nervous system in 5. Tumour cells were seen in the lymphatics and in the alveolar spaces, in 3 cases in the alveolar spaces of the opposite lung as well.

Surgery was not considered feasible in 9 cases. There was no evidence that chemotherapy or radiotherapy modified the course of the disease in the 3 patients who received such treatment. The mean survival period in this non-surgical group was 11 months. The remaining 12 patients underwent lobectomy or pneumonectomy. In this group the mean survival period was 27 months, with extremes of one week to 9 years. Those treated by pneumonectomy survived an average of 3·8 years, and those subjected to lobectomy 15 months.

The commonly employed diagnostic methods appeared to be of little help in this particular tumour. The authors consider that the most reliable diagnostic technique is exploratory thoracotomy. Appreciable survival without surgery has not been reported. The early employment of adequate resection would appear to be the only available therapy.

G. Clayton

1210. **Medical Management of Advanced Lung Cancer.** [Review Article]
R. B. GOLBEY. *Medical Clinics of North America* [*Med. Clin. N. Amer.*] **45**, 627–641, May, 1961. 3 figs., 25 refs.

1211. **A Review of Some Important Problems Concerning Lung Cancer. Part I: Considerations of Epidemiology, Etiology and Pathogenesis**
N. C. DELARUE. *Canadian Medical Association Journal* [*Canad. med. Ass. J.*] **84**, 1374–1385, June 17, 1961. Bibliography.

Endocrinology

1212. **Effects of Growth Hormone on Calcium and Magnesium Metabolism**
S. HANNA, M. T. HARRISON, I. MACINTYRE, and R. FRASER. *British Medical Journal* [*Brit. med. J.*] **2**, 12–15, July 1, 1961. 2 figs., 18 refs.

At the Postgraduate Medical School (Hammersmith Hospital), London, the authors have studied the effects of growth hormone from human and bovine pituitary glands on calcium and magnesium metabolism.

An acromegalic patient was studied before and after implantation of radioactive gold into the pituitary fossa. Before the implant there was a high urinary excretion of calcium. After pituitary destruction this fell to normal levels and the amount of calcium absorbed from the gut was diminished despite a greater intake. Intestinal absorption of magnesium was also diminished after pituitary destruction.

Injections of growth hormone were given to 6 patients, 4 of whom had hypopituitarism, one malignant disease with pituitary ablation, and one osteoporosis. In 5 patients there was a rise in urinary excretion of calcium, and in 3 a similar rise in magnesium excretion. Faecal loss of magnesium was diminished in all cases, while that of calcium was also diminished, but to a less definite degree.

The authors conclude that the effects on calcium and magnesium metabolism both of administration and of excessive secretion of growth hormone resemble the effects of vitamin-D administration. *Charles Rolland*

1213. **The Various Types of Thyroid Malfunction in Cretinism and Their Relative Frequency**
E. A. CARR JR., W. H. BEIERWALTES, J. V. NEEL, R. DAVIDSON, G. H. LOWREY, V. N. DODSON, and J. H. TANTON. *Pediatrics* [*Pediatrics*] **28**, 1–16, July, 1961. 1 fig., 47 refs.

A comprehensive clinical and biochemical study of 56 cretins has been made at the University of Michigan Medical School, Ann Arbor. These included 41 born after the introduction of iodized salt for general use in the State of Michigan.

The minimum incidence of thyroid glands in the cretins was 21%, and the probable incidence 32%. A thyroid gland was considered to be present when the gland was palpable, found at surgery, demonstrable by scintigram, showed a net radioactive iodine uptake over the thyroid area of more than 10%, or incorporated radioactive iodine into circulating compounds. Inability of the thyroid gland to take iodine into an organic form was detected by discharge of radioactive iodine after the administration of potassium thiocyanate to 6 patients, and chromatography of the thyroid-gland hydrolysates in 4 patients. Serial studies of thyroidal function indicated that progressive post-natal failure of thyroid function may result in athyreosis. *G. B. West*

1214. **Antithyroid Drugs in the Treatment of Hyperthyroidism**
J. C. MCCLINTOCK, F. X. GASSNER, N. BIGELOW, and W. A. BAKER. *Surgery, Gynecology and Obstetrics* [*Surg. Gynec. Obstet.*] **112**, 653–658, June, 1961. 10 figs., 9 refs.

The authors describe their experience during the past 15 years with the use of 3 antithyroid drugs—propylthiouracil, methimazole (" tapazole ", " mercazole ") and iodothiouracil (" itrumil ")—in the treatment of 843 hyperthyroid patients. Medical cure—that is, permanent remission without significant increase in the thyroid enlargement due to the drug treatment—followed in 17 (14%) of 120 patients treated with propylthiouracil, 25 (15%) of 164 treated with methimazole, and 61 (11%) of 559 given iodothiouracil. The optimum duration of treatment for this purpose is thought to be 18 months. The incidence of toxic manifestations was 8% with propylthiouracil, 6% with methimazole, and 5% with iodothiouracil. A serious reduction in the circulating neutrophil count occurred in 5 patients (none of whom received iodothiouracil); one of these died of agranulocytosis.

The authors regard iodothiouracil as the drug of choice for preoperative preparation because of its lower toxicity (although this may be equalled by carbimazole, of which their experience was necessarily very limited) and because of the improvement from the surgeon's point of view in the texture of the gland. They have found that after preparation with iodothiouracil alone the thyroid tissue is less friable and vascular and more easily resectable than after preparation with any of the other drugs plus iodide.

Hypertrophy of the glandular epithelium is characteristic of hyperthyroidism; microscopical measurements of the mean thyroid acinar-cell height in operative specimens were therefore compared after preoperative treatment with various drugs. This method confirmed that satisfactory involution followed treatment with iodothiouracil, but did not show a clear advantage in the use of this rather than any other method of preparation. The authors review some of the literature dealing with iodothiouracil. They base their advocacy of its use for preoperative preparation upon their operative findings of a more normal texture of the thyroid and of a lower incidence of drug-induced enlargement of the gland.

H.-J. B. Galbraith

1215. **Diagnosis of Hyperparathyroidism**
P. PRONOVE and F. C. BARTTER. *Metabolism: Clinical and Experimental* [*Metabolism*] **10**, 349–363, May [received July], 1961. 8 figs., 29 refs.

Attempts at clarification of the diagnosis of hyperparathyroidism involve studies of renal tubular reabsorption of phosphate (T.R.P.), the response to

exogenously administered calcium, and the response to phosphorus deprivation. At the National Heart Institute, Bethesda, Maryland, the authors investigated the values for T.R.P. and response to calcium infusion in 16 normal subjects and in 20 patients with confirmed hyperparathyroidism. In 9 of the patients with hyperparathyroidism the serum calcium level was above normal, in 7 the serum phosphorus level was below normal, and in 12 the urinary calcium excretion was above normal, but in only 4 were all these three values abnormal. The subjects were studied while receiving three dietary regimens: (1) 500 mg. of phosphate daily with addition of aluminium hydroxide to lower the phosphate intake still further; (2) the normal hospital diet; and (3) the normal diet plus sodium phosphate supplement given in four 6-hourly doses to supply from 2 to 4 g. of phosphorus daily. Phosphate clearance was determined at least three times during the control period, inulin clearance being measured at the same time. The serum phosphate level was then artificially raised by a dose of neutral phosphate and thereafter 35 minutes was allowed for equilibration before urine was collected over four 20-minute periods.

In the 20 cases of hyperparathyroidism and the 16 normal subjects the phosphate clearance was shown to be directly related to the phosphorus intake. In 7 patients with hyperparathyroidism and 6 normal subjects the ratio of T.R.P. to glomerular filtration of phosphorus (G.F.P.) was shown to be an inverse function of phosphorus intake, and a low index could not be regarded as a necessary accompaniment of hyperparathyroidism. The TmP (maximum tubular reabsorption of phosphate), determined in 12 patients with hyperparathyroidism and 7 normal subjects, showed considerable overlap and seemed to correlate closely with the glomerular filtration rate. For the calcium infusion test all patients received a constant liquid diet for 4 days, urinary specimens being collected from the second day onwards. On the third day an infusion of calcium glucoheptonate containing 15 mg. of calcium per kg. body weight was given over 4 hours to 18 of the patients and 6 normal subjects. On the day following this infusion all the normal subjects showed a rebound increase in urinary phosphate value, varying from 12% to 57% over the control day. Of the 18 patients, the urinary phosphate excretion on the day after the infusion was lower than control values in 9, while in the remaining 9 there was a failure of the urinary phosphorus rebound. It is considered that this test is a valuable adjunct in the diagnosis of hyperparathyroidism. *B. M. Ansell*

1216. **Production of Hypercalciuria by Phosphorus Deprivation on a Low Calcium Intake: a New Clinical Test for Hyperparathyroidism**

P. Pronove, N. H. Bell and F. C. Bartter. *Metabolism: Clinical and Experimental* [*Metabolism*] **10**, 364–371, May [received July], 1961. 4 figs., 4 refs.

The authors have shown [see Abstract 1215] that the oral administration of phosphate can reverse the chemical abnormalities of hyperparathyroidism, namely hypercalcaemia, hypophosphataemia, and hypercalciuria, while administration of a low phosphorus diet can cause a rise in the serum calcium and a decrease in the serum phosphate levels. This further study reports the results of phosphorus deprivation during low calcium intake. Ten normal subjects and 18 patients with hyperparathyroidism, subsequently confirmed surgically, were given a diet containing 500 mg. of phosphorus and 200 mg. of calcium for 13 days, with the addition of aluminium hydroxide before meals for the last 10 days. On this standard diet the serum calcium level was raised in 9 patients, the serum phosphorus level was low in 9, and the urinary calcium content raised in 11; these factors were all abnormal in only 4 subjects and all were normal in 2. After 3 days for equilibration serum specimens were obtained daily before breakfast and 24-hour urine specimens were analysed for calcium and phosphorus content. In 2 of the normal subjects the study was repeated during administration of parathyroid extract (50 to 100 units intramuscularly twice a day), while in 5 of the patients with hyperparathyroidism it was repeated following surgical cure of their condition.

Although the serum calcium and phosphorus levels showed variable change, reduction in urinary phosphorus excretion occurred in all subjects during this period. The urinary calcium excretion exceeded 250 mg. per day in all the patients with hyperparathyroidism, but in the normal subjects it did not rise above 230 mg. per day. An abnormal test result was defined as a rise in the urinary calcium level above 250 mg. daily regardless of the changes in the serum calcium and phosphorus levels. Following cure of their hyperthyroidism the test result was normal in the 5 subjects studied postoperatively. Administration of parathyroid extract to the 2 normal subjects produced an abnormal phosphorus deprivation reaction, but the classic chemical abnormalities of hyperparathyroidism were not produced.

It is suggested that this test, together with the response to calcium infusion, is of the greatest value in confirming a diagnosis of hyperparathyroidism. *B. M. Ansell*

ADRENAL GLANDS

1217. **Blood Corticotropin (ACTH) Levels in Cushing's Disease**

W. C. Williams Jr., D. Island, R. A. A. Oldfield Jr., and G. W. Liddle. *Journal of Clinical Endocrinology and Metabolism* [*J. clin. Endocr.*] **21**, 426–432, April, 1961. 1 fig., 14 refs.

A study has been made at the Vanderbilt University School of Medicine, Nashville, Tennessee, to determine whether the pituitary gland secretes abnormal amounts of corticotrophin (ACTH) in Cushing's disease.

It was postulated that if the primary disorder in Cushing's disease were a derangement of pituitary function it would not be correctable by adrenalectomy. In such cases it should then be possible to control plasma cortisol levels while observing plasma ACTH levels. Two groups of patients were studied: 10 who had previously undergone bilateral adrenalectomy as a treatment for Cushing's disease and a control group of 8 patients with Addison's

disease without a previous history of Cushing's disease. While the two groups differed fundamentally as regards the presence of Cushing's disease, they were alike in that both lacked adrenal function.

The plasma hydroxycorticosteroid levels were comparable in the two groups. However, plasma ACTH levels as measured by a bioassay technique were found to be consistently higher in the patients who had been subjected to adrenalectomy for Cushing's disease. It is concluded that excessive secretion of ACTH in Cushing's disease provides an explanation for all the known features of the disorder and there is at present no evidence to support the hypothesis that Cushing's disease is an intrinsic adrenal disorder.

I. McLean Baird

1218. **Hypoglycaemia and Abnormal Steroid Metabolism in Adrenal Tumours**
R. WILLIAMS, A. E. KELLIE, A. P. WADE, E. D. WILLIAMS, and T. M. CHALMERS. *Quarterly Journal of Medicine* [*Quart. J. Med.*] **30**, 269–284, July, 1961. 5 figs., 46 refs.

The authors describe their observations in 3 cases of carcinoma of the adrenal cortex, of which one was seen at Hammersmith Hospital and 2 at the Middlesex Hospital, London. None of the patients showed the classic picture of Cushing's syndrome or adrenal virilism, but in all 3 the urinary excretion of 17-ketosteroids and 17-hydroxycorticosteroids was high. A remarkable feature of all 3 cases was the presence in the urine of large amounts of the tetrahydro derivative of Reichstein's Compound S. It is thought probable that this finding indicated a defect in 11 β-hydroxylation, since it is by this process that Compound S is normally converted to cortisol. It was noted, however, that the excretion of tetrahydro cortisol was also high. Hypertension was present in 2 of the patients; hypertension has been regarded by other workers as the distinguishing feature of the type of congenital adrenal hyperplasia in which there is a defect in 11 β-hydroxylation. In 2 patients hypoglycaemia was the main clinical feature and there is little doubt that it was due to the tumour, since it disappeared in one case after the tumour was removed but reappeared when metastases developed; the tumour was not removed in the second patient. The hypoglycaemia did not appear to be due to the abnormal steroid production, and it is suggested that it may have been the result of excessive uptake of glucose by the tumour mass.

P. A. Nasmyth

1219. **Adrenal Steroids and Infection: the Effect of Cortisone Administration on Polymorphonuclear Leukocytic Functions and on Serum Opsonins and Bactericidins**
J. G. HIRSCH and A. B. CHURCH. *Journal of Clinical Investigation* [*J. clin. Invest.*] **40**, 794–798, May, 1961.

There is much evidence that cortisone administered in large doses increases susceptibility to infection, but the mechanism of this action is unknown. This paper from the Rockefeller Institute, New York, describes experiments designed to test the effects of cortisone on the function of certain defence systems, namely polymorphonuclear leucocytes and such serum factors as bactericidins, opsonins, complement, and antibody. Young adult New Zealand red rabbits were given cortisone intramuscularly in doses of 25 mg. per kg. body weight for 11 days, blood being obtained by cardiac puncture before and at the end of the cortisone injections and the serum frozen and stored. Peritoneal exudates provoked by the intraperitoneal injection of glycogen were also obtained and the polymorphonuclear leucocytes in them harvested and tested for: (1) their ability to ingest and kill *Staphylococcus albus* and *Salmonella typhimurium*; (2) any changes in cell morphology before and after ingestion of the microorganisms; and (3) their content of certain bactericidal agents extracted from them, namely lysozyme, phagocytin, and histones.

It was found that leucocytes obtained from these rabbits did not differ appreciably in any of the ways mentioned above from those obtained from a control group of normal rabbits. Similarly, serum opsonic power (measured by serial dilution of the serum) and serum bactericidins (estimated by the technique described by Hirsch (*J. exp. Med.*, 1960, **112**, 15), using coliform bacteria) were not altered by the administration of cortisone, indicating that antibodies and complement were not suppressed. The authors suggest that the steroid lowers host resistance by suppressing the normal inflammatory response and perhaps also by producing some change in metabolism which is favourable to microorganisms.

Nancy Gough

1220. **Late Para- or Post-puberal Virilism.** (Les virilismes tardifs para ou post-pubertaires)
J. DECOURT, M. F. JAYLE, E. E. BAULIEU, and P. MAUVAIS. *Semaine des hôpitaux de Paris* [*Sem. Hôp. Paris*] **37**, 1825–1834, June 2, 1961. 12 figs., 18 refs.

Congenital hyperplasia of the adrenal cortex, which is revealed in young girls by the appearance of pseudohermaphroditism or by precocious masculine-type puberty, is usually attributable to a congenital absence of a 21-hydroxylase. Absence of this enzyme leads to faulty or absent synthesis of cortisol, with consequent excess production of corticotrophin. This in turn produces the hyperplasia and excessive secretion of adrenal androgens and of 17-hydroxy- and 11-17-dihydroxyprogesterone. Metabolites of the latter (pregnanetriol and pregnanetriolone) appear in the urine.

Virilizing symptoms appearing at, or after, puberty have more diverse aetiology. The various causes are classified and considered and 6 illustrative cases seen at the Hôpital de la Pitié, Paris, are presented. The authors outline the clinical symptoms to be assessed (degree and distribution of hair and various signs of Cushing's syndrome) and the biochemical tests to be carried out, including estimation of urinary 17-oxysteroids, 17-hydroxycorticosteroids, dehydro-epi-androsterone, the pregnanediol complex, and phenolic steroids; chromatographic fractionation of these and estimation of acetaldehydrogenic steroids; and the effects of corticotrophin and chorionic gonadotrophin and of corticotrophin inhibition by dexamethasone.

Virilism may be associated with other symptoms of overactivity of the adrenal cortex or with acromegaly.

The high rate of steroid production in adrenocortical tumours is unaffected by corticotrophin or dexamethasone, whereas that in adrenocortical hyperplasia is differentially affected, 17-oxysteroid excretion being little affected while 17-hydroxycorticosteroid output is greatly increased or may be slightly decreased. Some cases of obesity with virilization and signs of adrenocortical overactivity are of purely hypophysial origin and amenable to dexamethasone treatment. In rare cases virilism *per se* without associated symptoms may be caused by an adrenocortical tumour as shown by greatly increased dehydro-epi-androsterone output. More commonly it is due to adrenocortical hyperplasia with moderately increased output of dehydro-epi-androsterone *or* of the pregnanediol complex; both values are restored to normal by treatment with dexamethasone. Virilism of ovarian origin is rarer and may be caused by various ovarian tumours (arrhenoblastoma or Leydig-cell tumour), in which case the urinary 17-oxysteroid output is raised, chiefly by excretion of aetiocholanolone and androsterone, and is unaffected by corticotrophin inhibition. Non-neoplastic ovarian abnormalities may also cause virilism, but then there is little or no increase in 17-oxysteroid excretion, while cases of idiopathic virilism have been described in which steroid excretion was apparently normal. *Peter C. Williams*

1221. **Static and Dynamic Investigation of Androgenic Endocrine Function in the Female.** (L'exploration statique et dynamique de la fonction endocrine androgénique chez la femme)
J. MAHAUX and M. NAGEL. *Semaine des hôpitaux de Paris* [*Sem. Hôp. Paris*] **37**, 1841–1847, June 2, 1961. 4 figs., 12 refs.

In investigating androgenic endocrine function in the female the authors recommend that the following urinary determinations be performed: neutral 17-oxosteroids, total reducing corticoids, 17-hydroxycorticoids, 17-oxogenic steroids, pregnanetriol, and oestrone. In addition, the urinary 17-oxosteroids should be chromatographically fractionated. In 27 cases of hirsutism in young women with some degree of virilism and in 3 cases of amenorrhoea with masculine somatotype seen at the Brugman and Etterbeek Hospitals, Brussels, the urinary excretion of 17-oxosteroids was high and was reduced in all cases by treatment with prednisolone, given with the aim of inhibiting corticotrophin secretion. The increase in 17-oxosteroids was not always in the same fractions, though dehydro-epi-androsterone and/or 11-oxy-17-oxosteroids were most commonly affected. These facts indicate that the oxosteroids excreted in increased amounts are of adrenal origin.

Adrenal cortical stimulation by administration of exogenous corticotrophin need not be only by intravenous injection, as intramuscular injections of corticotrophin–zinc phosphate can be used. The responsiveness of the hypothalamic–hypophysial–cortical pathways can be tested by noting the increase in steroid excretion after suppression with "metopiron" (SU4885), that is, the rebound phenomenon. If the urinary excretion of 17-oxosteroids of adrenal origin is unaffected by prednisolone or corticotrophin then an adrenal tumour is probably present. If the urinary oxosteroids are chiefly androsterone and aetiocholanolone, an ovarian origin is likely, and this can be tested by treatment with prednisolone or dexamethasone, which will not reduce the output of these steroids, and with chorionic gonadotrophin, which will reduce it. *Peter C. Williams*

1222. **Aldosteronism and Hypertension: Primary Aldosteronism versus Hypertensive Disease with Secondary Aldosteronism.** [Review Article]
J. W. CONN. *Archives of Internal Medicine* [*Arch. intern. Med.*] **107**, 813–828, June, 1961. 1 fig., bibliography.

PANCREAS

1223. **Glucose and Cortisone–Glucose Tolerance in Normal and "Prediabetic" Humans**
T. H. LAMBERT, R. B. JOHNSON, and G. R. PAUL. *Annals of Internal Medicine* [*Ann. intern. Med.*] **54**, 916–923, May, 1961. 3 figs., 9 refs.

The standard glucose tolerance test before and after administration of a cortisone load was investigated in 175 subjects at the Scripps Clinic and Research Foundation, La Jolla, California. Included were 92 apparently healthy controls with no family history of diabetes and 83 subjects who were not clinically diabetic but blood relatives of known diabetics. The glucose tolerance test was preceded by a 300-g. carbohydrate diet for 3 days; the glucose load was 1·75 g. per kg. body weight and the cortisone load was 50 mg. 8½ and 2 hours before the test (62·5 mg. of cortisone if body weight exceeded 160 lb. or 72·575 kg.). Blood glucose levels were estimated fasting and at half-hourly intervals for 3 hours by a modified Somogyi–Nelson method. "Normal" blood sugar levels for the test were established by analysing the results in the controls. Values within 2 standard deviations of the mean were regarded as normal, within 2 to 3 standard deviations as borderline, and over 3 standard deviations as frankly diabetic.

Of the 92 control subjects, 3 were frankly diabetic and 4 borderline by the standard glucose tolerance test, and of the latter, 3 became frankly diabetic with a cortisone load; of the remaining 85 control subjects, 58 were given a cortisone load and 4 (7%) of these became frankly diabetic. Of the 83 relatives of diabetics, 5 showed frankly diabetic curves and 4 were borderline, 2 of the latter becoming frankly diabetic with cortisone; and of the remaining 74, 10 became frankly diabetic with cortisone. There was no significant difference in the response to cortisone between the subjects with and without a family history of diabetes, and the authors suggest that the cortisone–glucose tolerance test is not necessarily specific in detecting prediabetes in subjects with a diabetic family history.

[This is a confusing paper, mainly owing to the difficulty in sorting out from the text the numbers of patients in the different groups actually undergoing the tests—the most helpful way is by studying the authors' diagram, Fig. 3.] *Gerald Sandler*

1224. **Gestational Diabetes: Unsuspected, Asymptomatic Diabetes in Pregnancy**
J. B. O'SULLIVAN. *New England Journal of Medicine* [*New Engl. J. Med.*] **264**, 1082–1085, May 25, 1961. 1 fig., 13 refs.

The authors have attempted to determine the frequency of asymptomatic diabetes occurring during pregnancy (gestational diabetes) and its relation to the subsequent development of diabetes.

All women registering at the antenatal clinic at Boston (Massachusetts) City Hospital between April, 1954, and December, 1959, were screened. A glucose tolerance test was carried out when one or more of the following criteria were present: venous blood sugar level of 130 mg. per 100 ml. or more one hour after 50 g. glucose by mouth; a family history of diabetes; a history of having borne a baby weighing 9 lb. (4·082 kg.) or more; and a history of foetal death, neonatal death, congenital anomaly, or prematurity toxaemia in two or more pregnancies. Diabetes was considered to be present " if any three or more or if the fasting and 3-hour blood sugars met or exceeded the following levels: fasting, 110 mg., at one hour, 170 mg., at 2 hours, 120 mg., and at 3 hours, 110 mg. per 100 ml.".

Of 20,070 antenatal cases screened, 8,344 (41·5%) were found positive to one or more of the criteria upon initial screening. Of these, 7,061 (85%) had glucose tolerance tests, and 146 (0·73% of all cases registering) revealed the defined level for gestational diabetes. Six weeks to 6 months after delivery 126 of these 146 women had further glucose tolerance tests, and 9 (7·1%) met the diagnostic criteria for diabetes mellitus. Extension of the period up to 5½ years revealed that 39 (28·5%) of the 137 patients available for study had become diabetic. Glucose tolerance tests were also carried out in subsequent pregnancies when possible, but of 38 such cases, only 14 again reached the level of gestational diabetes and one woman showed gestational diabetes during her first, second, and fourth pregnancies, but the blood sugar level remained normal in the third.

These observations indicate that gestational diabetes occurs about once in 116 pregnancies, whereas overt diabetes is met with only about once in 500 or even 1,000 pregnancies, according to different authors. Thus gestational diabetes appears to be 4 to 8 times more common than overt diabetes in pregnancy.

In view of the fact that 93% of the patients no longer exhibited abnormal glucose tolerance post partum, it might be argued that the earlier glucose tolerance curves should be accepted as within the normal range produced by pregnancy in a woman without predisposition to diabetes. Numerous studies have, however, been made to determine the effect of pregnancy on the glucose tolerance test, and in the majority no more than a delayed peak was observed. Furthermore, the later follow-up of the patients with gestational diabetes revealed that diabetes developed in 28·6% within the 5½-year period. This is a minimum figure, since many patients were not followed to the end-point for various reasons, and the use of the life-table technique provides compensation for such losses. As applied to this study the cumulative incidence of diabetes developing from gestational diabetes would be 11% at one year, 24% at 2 years, 32% at 3 years, 42% at 4 years, and 67% at 5½ years.

The authors' findings demonstrate that diabetes can appear temporarily in pregnancy as early as 5½ years before it becomes overt. Experience with glucose tolerance tests in subsequent pregnancies appears to be in keeping with the fluctuating course of early diabetes, but the continuing development of overt diabetes among these patients makes them prediabetic beyond any doubt. They are therefore suitable subjects for study of the disease while it is still latent and yet easily recognizable. The far-reaching possibilities of prevention are dependent on such early recognition.

John Lister

1225. **Survival of Diabetics with Proteinuria**
F. I. CAIRD. *Diabetes* [*Diabetes*] **10**, 178–181, May–June, 1961. 1 fig., 13 refs.

This study must be taken in conjunction with a series of community studies in Birmingham where a previous analysis of the population in the city has rendered possible comparisons between hospital populations and a normal city population. The author selected his material from the patients attending the diabetic clinic at the General Hospital, Birmingham, between January, 1946, and March, 1949; 134 were selected who showed persistent proteinuria and were followed until October, 1959 —that is, for a 10-year period. Proteinuria initially was defined as a positive reaction to boiling and to salicylsulphonic acid on at least two occasions within 3 years of each other. The criteria for deciding the time of onset of proteinuria and for selecting the control group are given. The survival rate of diabetic patients with proteinuria after 5 years was 65% compared with 73% for all diabetics and 83% for the controls. After 10 years the survival rate was 28% for diabetics with proteinuria, 46% for all diabetics, and 61% for the controls. Allowing for standard errors, it is suggested that the prognosis for diabetic patients with proteinuria is not quite so poor as most previous authors have suggested.

R. E. Tunbridge

1226. **Clinical Evaluation of Tolcyclamide in Treatment of Diabetes Mellitus**
J. J. PAULLADA and J. L. DEL VILLAR. *Metabolism: Clinical and Experimental* [*Metabolism*] **10**, 221–230, March, 1961. 8 figs., 34 refs.

The authors report from the General Hospital of Mexico City a trial of a new hypoglycaemic sulphonylurea, 1-*cyclo*hexyl-3*p*-tolylsulphonylurea (tolcyclamide), in the treatment of 32 diabetics aged 21 to 72 years. The patients were divided into two groups according to the duration of their diabetes; the first group consisted of 15 patients with diabetes of less than 5 years' duration and the second group of 17 patients with diabetes of longer duration than this. In Group 1 0·5 g. of tolcyclamide 3 times a day reduced blood sugar levels to normal in 11 patients, and doubling the dose reduced the fasting blood sugar level to below 120 mg. per 100 ml. in all the remaining patients except one juvenile diabetic.

In Group 2 the results were less satisfactory, only 6 of the patients responding well to 1·5 g. of the drug daily and only 2 more to 3 g. daily. *K. O. Black*

1227. **Clinical Effectiveness and Toxicity of Metahexamide in Treatment of Diabetes Mellitus**
I. A. Feder and A. Kahn. *Metabolism: Clinical and Experimental* [*Metabolism*] **10**, 246–260, March, 1961. 3 figs., 8 refs.

Metahexamide, a sulfonylurea compound, was administered to 22 patients with diabetes mellitus (22 to 82 years of age), 21 of whom were stable diabetics. Good diabetic control (mean fasting blood sugar below 160 mg. %) was attained in only 50% of the cases. Duration of treatment ranged from 2 weeks to 5 months. The usual dose of metahexamide was 100–200 mg. per day. Evidence of hepatic dysfunction was observed in 10 patients, 3 of whom showed histologic evidence of hepatic damage by liver biopsies. Clinical jaundice occurred in one patient. Less serious side effects, such as weakness, anorexia, nausea, diarrhea, vertigo, pruritus, dermatitis and eosinophilia, developed in 8 patients. It is concluded that metahexamide is not completely effective as a hypoglycemic agent and is too toxic to be utilized in treating diabetes mellitus.—[Authors' summary.]

1228. **Study of Glyhexylamide, a New Hypoglycaemic Sulphonamide.** (Étude clinique d'un nouveau sulfamide hypoglycémiant: le glyhexylamide)
J. Lebon, R. Claude, M. Leutenegger, and A. Lacroix. *Diabète* [*Diabète*] **9**, 151–157, April–May, 1961.

The authors have studied the action of glyhexylamide (4-methyl-3-aminobenzol sulphamyl *cyclo*hexyl carbamide; "isodiane") in diabetics treated in private practice in Algiers. This sulphonamide is an arylsulphonylurea and has the following pharmacological characteristics: it has 10 times more hypoglycaemic effect than other sulphonamides, its action lasts for 25 hours, it has very low toxicity, is very soluble, and has no bacteriostatic effect on intestinal flora. The 77 patients treated were given 100 to 200 mg. daily of the drug initially and after 15 days according to need, the stabilizing dose ranging from 50 mg. (15 cases) to 200 mg. daily (37 cases).

After one month results were good in 79%, but this figure fell to 70% after several months. Results were better in patients over 40 years of age (48 out of 66) with diabetes of recent development, in those who had previously required insulin in a dosage of less than 30 units daily and had not been given insulin for more than a year, and also in untreated diabetics (13 out of 16). A few patients who had not responded to other sulphonamide derivatives were also successfully treated. Results were poor in young patients, long-standing diabetics, under-nourished patients, and those with complicating tuberculosis (but good in the presence of vascular lesions). A few patients showed transitory neutropenia and microscopic haematuria, but there were no other toxic or allergic phenomena. The drug was considered to be superior to other sulphonamide hypoglycaemic agents, especially in recent, mild, and middle-aged diabetics [and is worth further trial]. *Arnold Pines*

1229. **Value of N-N-Dimethyl Guanyl Guanide in the Treatment of Diabetes Mellitus.** (Intérêt du N.N. diméthyl guanyl guanidine dans le traitement du diabète sucré)
J. Lebon, R. Claude, M. Leutenegger, P. Galley, and J. Tricoire. *Diabète* [*Diabète*] **9**, 159–169, April–May, 1961.

The authors have treated 54 diabetics with a diguanide compound, "glucophage", the daily dose of which was between 2 and 3 g. Of 14 florid diabetics in their fifties, the results were good in 9 (65%), often in combination with sulphonamides even when these latter alone had failed previously. The remaining patients were severe diabetics who had usually been receiving more than 60 units of insulin daily. In a few of them the dose of insulin could be reduced, and in 8 the previous dose of insulin now gave much better control; in only 45% of all these patients, however, were the results worth while. The drug had to be stopped in 4 cases because of severe gastro-intestinal disturbances and in one because of an allergic erythema; there were no other severe toxic effects. It was difficult to predict the action of the drug, since in some patients it was successful, but failed in other identical cases.

The authors consider that the drug is equal in effect to the sulphonylurea compounds, but that the toxic effects make it of second choice only. It appears to be most effective in middle-aged florid diabetics in whom it may be effective when sulphonamides are ineffective or are not tolerated, and it is particularly useful in supplementing the action of insulin even in cases of severe diabetes. *Arnold Pines*

1230. **The Mode of Action of Diguanides in Diabetes Mellitus.** (Zur Frage der Wirkungsweise der Biguanide beim Diabetes mellitus)
W. Höpker. *Klinische Wochenschrift* [*Klin. Wschr.*] **39**, 588–590, June 1, 1961. 17 refs.

Previous studies have shown that the sulphonylurea drugs, through their β-cytotrophic activity, induce the β cells of the pancreas to increase their production of insulin. On the other hand the diguanides influence the enzymatic system of the liver and so decrease the production of glucose, at the same time taking a part in peripheral cellular metabolism by inhibiting glycolysis extrahepatically. For this reason the diguanides are valuable in the treatment of patients with diabetes which cannot be controlled by the sulphonylureas.

In this paper a thorough clinical trial with dimethyldiguanide is reported from the Municipal Hospital, Lüdenscheid, Germany. This drug is considerably less toxic than the other known diguanides and although less effective, dose for dose, it can be administered in larger quantities on account of its significantly lower toxicity. Doses of up to 3 g. were well tolerated, and out of 40 patients only 3 showed some intolerance. Toxicity, allergy, and ketosis were not observed during the trial. No difference was found between the mode of action of dimethyldiguanide and that of carbutamide or metahexamide. A few cases of "delayed failure" were observed. In the cases of diabetes which could not have

been treated with a sulphonylurea, a 22% saving in insulin was achieved. However, placebos administered to diabetic controls resulted in a 15% saving in insulin. It is therefore deduced that dimethyldiguanide has a β-cytotrophic activity, but that its extra-insular effect, which can be utilized in diabetics who cannot be treated with oral antidiabetic drugs, is rather low.

S. M. Hardy

1231. **Evaluation of Sorbitol in the Diet of Diabetic Children at Camp**

J. Steinke, F. C. Wood Jr., L. Domenge, A. Marble and A. E. Renold. *Diabetes* [*Diabetes*] **10**, 218–227, May–June, 1961. 7 figs., bibliography.

The opportunity was taken while diabetic children aged 5 to 15 years stayed at the Elliott P. Joslin Camp, Charlton, Massachusetts, to observe the effect of the addition of sorbitol to the diet upon insulin requirements, the blood and urine levels of glucose, and the blood levels of free fatty acids and ketones. The study group was composed of 143 campers and the control group of 62. The study was divided into three periods: an initial period of 2 to 4 days for stabilization, then a period varying from 8 to 48 days during which the 143 children received sorbitol, and a final phase of 5 days when no sorbitol was given. The maximum dose of sorbitol was 41 g. per day given in 3 doses. No significant changes were found in the degree of glycosuria, daily insulin requirements, or fasting blood values for sugar, ketone bodies, or free fatty acids. It is suggested that sorbitol may be preferable to fructose because of the lack of sorbitol metabolism during intestinal absorption. The slow rate of absorption probably accounts for the frequency of abdominal pain and diarrhoea, which are especially liable to occur following the use of larger doses.

It can only be concluded from the limited studies that quantities of sorbitol up to 41 g. daily can be given to juvenile diabetics without obvious improvement or deterioration in the control of their diabetes. Sorbitol in this dosage can therefore be used as an accessory supply of carbohydrates over a short period, but the authors are careful to emphasize that they have no data on the long-term effects and that even in the short-term experiment reported the parameters for assessing diabetic control were limited. *R. E. Tunbridge*

1232. **Phenformin as Adjuvant Oral Therapy in Diabetes**

A. Bloom and J. G. Richards. *British Medical Journal* [*Brit. med. J.*] **1**, 1796–1799, June 24, 1961. 2 figs., 9 refs.

Among 1,450 diabetics attending the Whittington Hospital, London, 255 (17·6%) were treated with oral hypoglycaemic agents. Primary and secondary failures were observed with both tolbutamide and chlorpropamide. In a group of 23 such patients small doses of phenformin (a diguanide) were tried, the phenformin being given in a dosage of 25 mg. three times a day or as a single 100-mg. slow-disintegration capsule. Nine patients responded to phenformin alone, but 14 responded only when the phenformin and sulphonylureas were given together. At a dose not exceeding 100 mg. daily, whether divided into smaller doses or given as a single slow-integration capsule, phenformin was well tolerated, though a number of patients complained of mild nausea, anorexia, and an unpleasant taste in the mouth.

A. I. Suchett-Kaye

1233. **The Management of Diabetes with the Aid of Oral Hypoglycemic Agents.** [Review Article]

L. P. Krall. *Medical Clinics of North America* [*Med. Clin. N. Amer.*] **45**, 823–838, July, 1961. 3 figs., 40 refs.

1234. **The Diagnostic Value of Sodium Tolbutamide in Hypoglycemic States**

S. S. Fajans, J. M. Schneider, D. E. Schteingart, and J. W. Conn. *Journal of Clinical Endocrinology and Metabolism* [*J. clin. Endocr.*] **21**, 371–386, April, 1961. 10 figs., 27 refs.

The authors of this paper from the University of Michigan Medical School, Ann Arbor, describe a new test for the diagnosis of functioning islet-cell tumours of the pancreas. Of 8 patients with this condition studied, the blood sugar response to 1 g. of sodium tolbutamide given intravenously was a rapid fall in level in all cases. The severe hypoglycaemia so produced persisted for 3 hours, while in 20 healthy subjects the blood sugar returned to its original level within 3 hours. The response to tolbutamide in 11 patients with functional hyperinsulinism was very similar to that in healthy subjects and clearly differentiated this disease from insuloma. It was considered that severe liver disease may cause a response similar to that of the patients with insuloma.

The authors conclude that the tolbutamide test is a helpful diagnostic procedure, but emphasize the need for caution in cases of suspected insuloma with fasting blood sugar levels in the hypoglycaemic range, recommending the administration of 50% glucose should severe symptoms recur. *I. McLean Baird*

1235. **Studies on Patients with Islet-cell Tumor, Including the Phenomenon of Leucine-induced Accentuation of Hypoglycemia**

G. C. Flanagan, T. B. Schwartz, and W. G. Ryan. *Journal of Clinical Endocrinology and Metabolism* [*J. clin. Endocr.*] **21**, 401–413, April, 1961. 3 figs., 23 refs.

This paper reports a careful investigation of the effect of the amino-acid leucine on 3 patients with islet-cell tumours of the pancreas carried out at the Presbyterian–St. Luke's Hospital, Chicago. Leucine was given in a dosage of 150 mg. per kg. body weight as a suspension in water and its effect compared with a similar dosage of glycine. The administration of leucine consistently provoked precipitate hypoglycaemia ranging from 21% to 76% below the fasting level. In some instances the experiment had to be stopped because of clinical manifestations of hypoglycaemia. On the other hand glycine caused no appreciable changes. After removal of the islet-cell tumour the precipitate fall in blood sugar level could not be produced with leucine.

On the basis of this evidence it is suggested that leucine acts by potentiating the peripheral action of insulin in patients with islet-cell tumour. *I. McLean Baird*

The Rheumatic Diseases

1236. **Combined Aspirin and Cortisone Treatment of Acute Rheumatic Fever: a Controlled Trial in Young Men**
J. D. H. SLATER. *Annals of the Rheumatic Diseases* [*Ann. rheum. Dis.*] **20**, 173–178, June, 1961. 1 fig., 17 refs.

The author describes a trial in which 28 young soldiers admitted to hospital in the Aldershot area suffering from rheumatic fever were treated with either aspirin alone or cortisone and aspirin combined. Therapy in each case was identical except for the addition of cortisone to the members of one group. Aspirin was given daily in five separate doses, the total dosage being 1 to 1½ grain per lb. (143 to 220 mg. per kg.) body weight per day, and blood salicylate levels were estimated 2 hours after the morning dose once weekly; these were usually of the order of 30 mg. per 100 ml. Cortisone was added in a dose of 300 mg. on the first day, with gradual reduction subsequently. For the first 10 days intramuscular penicillin was given and thereafter oral sulphadimidine, 1 g. daily. A standard and strict regimen was used for mobilization, this usually taking about 4 weeks, and the patient was not allowed to get up until 3 consecutive readings of the erythrocyte sedimentation rate (E.S.R.) taken at 4-day intervals were below 10 mm. in one hour (Westergren).

The findings indicated that fever and joint inflammation in young men were alleviated more rapidly by combined therapy than by aspirin alone, and that the E.S.R. also fell more rapidly with the combined regimen; there was, however, a transient rise in the E.S.R. in the steroid-treated patients on cessation of therapy.

D. Preiskel

1237. **Five-year Follow-up on Patients with Rheumatic Fever Treated by Bed Rest, Steroids, or Salicylate**
G. T. THOMAS. *British Medical Journal* [*Brit. med. J.*] **1**, 1635–1639, June 10, 1961. 8 refs.

A study is reported from the Canadian Red Cross Memorial Hospital, Taplow, Buckinghamshire, of 198 patients with rheumatic fever who were followed up for a minimum of 5 years and many for 6 to 10 years. Of the 198 patients, 125 who were admitted to hospital during the period 1948–50 were treated with rest in bed together with analgesics (in 111) and ACTH (corticotrophin), cortisone, or salicylates (in 14). None of the 125 received prophylaxis either in hospital or subsequently (unless they had a relapse). The remaining 73 patients, who were admitted in 1950–51, received a 6-week course of ACTH, cortisone, or salicylates in the cooperative clinical trial carried out by the Medical Research Council and the American Heart Association (*Brit. med. J.*, 1955, **1**, 555; *Abstr. Wld Med.*, 1955, **18**, 225). All 73 received prophylactic sulphonamide in hospital and after discharge. Of the 125 patients in the first group, 106 had no recurrence of rheumatic fever. Of these, 22 had no evidence of carditis in hospital and showed no abnormal clinical signs at 5 years, while 41 had slight carditis but at follow-up examination no serious heart disease, 31 having clinically normal hearts. The remaining 43 patients had marked signs of carditis in hospital and at 5 years the signs were normal in 2, unchanged in 30, diminished in 5, and more marked in 6. Of the 19 patients who had a recurrence, 4 were normal when last seen, in 3 the physical signs showed no change, in 3 they were less marked, and in 7 they were more marked; 2 patients had died. The severity of the heart lesion on admission to hospital was closely related to previous attacks. Patients who had had more than one attack tended to have serious cardiac lesions and those who had had three or more attacks were liable to show deterioration at the end of 5 years. The development of mitral stenosis was not observed except after three or more attacks.

There was no significant difference in the cardiac state between the 73 patients treated with ACTH, cortisone, or aspirin in the years 1950–51 and the 125 admitted in 1948–50 when their condition was assessed after 5 years, provided patients who had had recurrences were excluded. However, there were more recurrences in the group who received no prophylaxis and they fared less well than those who relapsed in the group given prophylaxis, the few recurrences in the latter group producing no lasting ill-effects on the heart.

It is concluded that treatment in hospital with steroids or salicylates has little effect on cardiac state at follow-up examination and that prophylaxis by preventing recurrences is the most certain way of reducing both morbidity and mortality from rheumatic fever.

C. Bruce Perry

1238. **The Treatment of Acute Rheumatic Fever**
A. DORFMAN, J. I. GROSS, and A. E. LORINCZ. *Pediatrics* [*Pediatrics*] **27**, 692–706, May, 1961. 6 figs., 36 refs.

A comparative study of the follow-up results (up to one year) of four regimens of treatment in active rheumatic fever (as defined by modified criteria of Duckett Jones) is reported in this paper from the University of Chicago. Because of the conflicting and often inconclusive results of earlier trials only first-attack cases with a duration of less than 19 days were included. Allocation to treatment groups was made at random and evaluation of murmurs was made without access to previous records.

The basic regimen (35 cases) was complete rest in bed for 15 weeks, penicillin injections for 5 days, and maintenance thereafter with sulphadiazine by mouth. In the other three regimens, each of which was given in 32 cases, the basic treatment was supplemented respectively by hydrocortisone, aspirin, and hydrocortisone together with aspirin for a period of 12 weeks. The dosage of steroids was adequate to produce marked hypercortisonism and in the last two groups mean blood salicylate

levels attained were 23·1 and 18·3 mg. per 100 ml. respectively. At the outset the patients in the four treatment groups were comparable in all important respects.

The immediate results showed a more rapid fall in temperature in the salicylate-treated group compared with patients given rest in bed and also in the steroid-treated patients compared with those given salicylate. However, by 15 weeks there was rise in temperature in over half of the steroid-treated patients compared with less than one-third of the patients in each of the other two groups. Other indices of disease activity such as the erythrocyte sedimentation rate and conduction time also showed this more rapid control in the salicylate- and steroid-treated groups.

The number of patients with congestive heart failure or pericarditis was too small for critical evaluation; heart size in all patients at the end of one year was within 20% of normal. The effect on the heart had therefore to be evaluated on murmurs. Apical systolic murmurs (" organic only "), present initially in 69% of the steroid-treated groups and 60% of the other two groups, were detected in 31% and 48% respectively at 15 weeks and in 14% and 38% at one year, a striking and significant difference (P=0·01). Of 46 patients without apical systolic murmurs initially (more or less equally divided between the 4 treatment groups), such murmurs had developed in only 3 at 15 weeks (2 in the aspirin-treated group and one in the bed-rest group), only one patient (aspirin-treated) having a residual murmur at one year. The incidence of diastolic murmurs was low, but the data showed a similar diminution at 15 weeks of apical and basal murmurs and at one year of basal diastolic murmurs in the steroid groups compared with the aspirin and bed-rest groups. Complications were few and slight except in 2 patients given steroid and aspirin in whom duodenal ulcers developed; the ulcer perforated in one and bled in the other, but in both patients the condition responded to treatment.

After a discussion, including [for good measure] a statement that chloramphenicol was ineffective (it was used in a preliminary study as more likely to prevent the formation of L forms), the authors conclude as follows: (1) patients without carditis may be safely treated with salicylates; (2) patients with carditis should be given adequate dosage of a steroid for 9 weeks, with gradual reduction of dosage thereafter; (3) all patients should have a bactericidal dosage of penicillin initially followed by prophylactic medication; and (4) there is no advantage in treatment with a steroid combined with aspirin.

[A careful study with a well balanced discussion.]

E. G. L. Bywaters

1239. **The Early Anemia of Acute Rheumatic Fever**
A. M. MAUER. *Pediatrics* [*Pediatrics*] **27**, 707–712, May, 1961. 2 figs., 11 refs.

The anaemia of the early stages of acute rheumatic fever has been variously ascribed to depressed erythropoiesis, haemolysis, and dilution of erythrocytes by increased plasma volume. The author of this paper from the University of Cincinnati, Ohio, has re-investigated this problem in 8 apparently well children and in 10 with rheumatic fever without congestive heart failure, using the dye dilution method (T-1824) for plasma volume and the radioactive chromium technique for erythrocyte volume. Only one of the 10 patients had had salicylate therapy for more than 3 days and 3 had had none; symptoms had lasted more than 10 days in 3 patients only.

The plasma volume was significantly increased in the patients compared with the controls (mean 59 ml. per kg. body weight compared with 45 ml. per kg.), the values being above the highest control reading in 5 of the 10 patients. A repeat estimation in 7 patients 10 to 80 days after the first showed a substantial decrease in plasma volume. There was no difference between 3 patients and 5 healthy controls in the rate of disappearance of dye in the first 30 minutes after injection, ruling out increased permeability or leakage. The half-life of erythrocytes in 3 patients ranged from 25 to 32 days, and no reticulocytosis was seen. In 3 patients there was good agreement between the results of the two methods of estimating blood volume.

It is concluded that the decreased haematocrit value in the early stage of rheumatic fever is due usually to dilution of the erythrocyte mass by an increased plasma volume.

E. G. L. Bywaters

CHRONIC RHEUMATISM

1240. **The Latex Fixation Reaction in Rheumatic and Non-rheumatic Diseases (Clinical and Serological Study).** (La réaction de fixation au latex (F. II L.P.) dans les affections rhumatismales et non rhumatismales (étude clinique et sérologique))
G. H. FALLET, E. MEYER, and J. J. SCHEIDEGGER. *Revue française d'études cliniques et biologiques* [*Rev. franç. Ét. clin. biol.*] **6**, 537–548, June–July, 1961. 3 figs., bibliography.

From the University Medical Clinic, Geneva, the authors report the results of a capillary tube latex fixation test in the examination of a large number of sera and compare the results for positive sera with those obtained with the slide test and a test using globulin fractions prepared by ammonium sulphate precipitation. The capillary tube method gave a positive result in 86% of 196 cases of classic and definite rheumatoid arthritis (by the criteria of the American Rheumatism Association), in 37% of 38 probable cases of rheumatoid arthritis, in none of 10 possible cases, and in one out of 6 of juvenile rheumatoid arthritis. Positive results were obtained in 29 out of 472 cases of other rheumatic diseases, including 2 out of 35 cases of gout, 2 out of 50 of ankylosing spondylitis, 6 out of 162 of arthrosis, 11 out of 30 of disseminated lupus erythematosus, 1 out of 3 of discoid lupus erythematosus, 2 out of 6 of scleroderma, and no positive results in 40 cases of rheumatic fever, 11 of psoriasis, 5 of Reiter's disease, 3 of dermatomyositis, 7 of arteritis, and 5 of Sjögren's syndrome. Of 505 non-rheumatic cases, 8·9% gave a positive result, most of these (45%) being cases of hepatic disease, while infec-

tions accounted for 16·6%, diabetes for 9·8%, malignancy for 6·4%, and Waldenström macroglobulinaemia for 12·5%; no positive results were obtained in 105 normal subjects. L.E. cells were found in 20 (15·4%) of 130 patients with confirmed rheumatoid arthritis, of whom all except one showed latex fixation.

The authors then took 24 cases of definite rheumatoid arthritis showing positive latex fixation titres (selected at random) and 19 similar cases showing negative titres and compared the two groups in respect of sex, age, and duration and severity of the disease; in regard to these factors no difference was found. However, changes in the sacro-iliac joints were found radiologically in 63% of the negative group as against 17% of the positive group. There was no significant difference in the serum protein pattern as shown either by paper or immuno-electrophoresis, though it is noted that the apparent increase in γ globulin noted on paper electrophoresis was not seen on immuno-electrophoresis. Gold treatment lowered the latex fixation test titre in 9 out of 10 cases. Diabetic patients with positive titres showed little difference from those with negative titres. Cases of liver disease with a positive titre showed a higher γ-globulin level and more β_2 M protein than did the negative-titre group. The latter protein was associated with agglutinating factor in liver disease, but not in rheumatoid arthritis or in diabetes.

E. G. L. Bywaters

1241. **Action of Long-term Chrysotherapy on the Evolution of Rheumatoid Arthritis.** (Action de la chrysothérapie à long terme sur l'évolution de la polyarthrite chronique évolutive)

J. Forestier, A. Certonciny, and F. Forestier. *Rhumatologie* [*Rhumatologie*] **13**, 69–80, March–April [received July], 1961.

This paper describes the results of gold therapy, a form of treatment originally introduced by the first-named author for the treatment of rheumatoid arthritis at Aix-les-Bains where during the past 25 years some 21,000 rheumatic patients have been treated, of whom 2,300 received chrysotherapy. Of the latter the authors have selected for study 435 well documented cases of rheumatoid arthritis of which 365 were in females. In all cases the diagnosis was confirmed clinically and biochemically over a period of 6 months. Treatment included at least 3 courses each of 0·1 to 1·5 g. of a gold salt given parenterally over 2 years or more. The minimum period of observation was 2 years, while 222 patients were observed for 5 years and 117 for 10 years. The usual form of treatment was with a compound containing 35 to 50% of metallic gold and the injections were given at intervals of 5 to 7 days, a preliminary dose of 50 mg. to test susceptibility being followed by regular doses of 100 mg. until a total of 1·2 to 1·5 g. had been given. The course was repeated after an interval of 6 weeks and again after 2 or 3 months, and further as indicated in individual cases.

The results were assessed according to three different modes of classification. (1) On a 3-point scale based on severity of symptoms with particular reference to fever, joint swelling, erythrocyte sedimentation rate, extent of involvement, anaemia, and weight loss; by these criteria at the beginning of treatment 10% of the patients were in Stage 1, 49% in Stage 2, and 41% in Stage 3 of evolution, but after 2 years' treatment, 48% were in Stage 1, 31% in Stage 2, and 11% in Stage 3. (2) Classification by degree of anatomical change showed that treatment did not have much effect in this respect. (3) The third method of assessment was by functional capacity on a 4-point scale. By this method the first and mildest group contained 2·7% of the patients at the start of treatment and 32% after 2 years, the second group 51·7% and 46·5% respectively, the third group 37% and 17%, and the fourth group 8·5% and 3·81% respectively. The authors thus conclude that although there is not much anatomical change, about 80% of patients are improved in regard to severity of the disease and functional capacity. The results after 5 and 10 years' treatment showed a similar trend of improvement in regard to severity of disease and functional capacity. Anatomical changes however are, as might be expected, progressive and an increasing number of cases fall into the groups with severe deformity in the course of time. Of the 435 patients, 145 (33·3%) showed some benign form of intolerance such as pruritus, evanescent erythema, or eczema, but treatment had to be stopped in only 10% of such cases. Visceral complications with evidence of hepatic, renal, or intestinal lesions occurred in 50 cases. There were 12 cases of agranulocytosis with thrombocytopenia and 2 of these were fatal. The authors point out that in this large series of cases the complications and side-effects were neither so common nor so serious as with steroid therapy and conclude that chrysotherapy is still the safest and most effective treatment for rheumatoid arthritis.

William Hughes

1242. **Rheumatoid Patients after Five or More Years of Corticosteroid Treatment: a Comparative Analysis of 183 Cases**

C. A. Berntsen and R. H. Freyberg. *Annals of Internal Medicine* [*Ann. intern. Med.*] **54**, 938–953, May, 1961. 1 fig., 4 refs.

The results of continuous, partially suppressive corticosteroid treatment over a period of 5 years or longer in 183 patients with rheumatoid arthritis are analysed in this paper from the New York Hospital–Cornell Medical Center and the Hospital for Special Surgery, New York. The average age of the patients was 51 years. Corticosteroids with proved antirheumatic activity were used as they were introduced, the first being cortisone acetate and the last dexamethasone. During the last 15 months of treatment more than half of the patients were taking either prednisone or triamcinolone. The aim was to give the smallest dosage which would produce partial suppression of the inflammation.

Functional changes were assessed according to the criteria of the American Rheumatism Association. After 5 years' treatment there was only a slight change in the percentage distribution of patients in the various stages, although the patients within those stages after treatment were not always the same as those who were there at the beginning, some having moved to an im-

proved stage and others having deteriorated. Structural changes were similarly classified; before treatment the patients were evenly divided between the four stages, but after 5 years 77% were in Stages III or IV. None of the patients showed structural improvement.

The authors were impressed with the finding that functional capacity was well maintained, but it was clear that structural changes were not halted. Serious complications of steroid therapy were frequent; there were 12 deaths in the series attributable wholly or partly to the treatment. *K. C. Robinson*

1243. **Psoriatic Arthritis. A Comparative Radiographic Study of Rheumatoid Arthritis and Arthritis Associated with Psoriasis**
V. WRIGHT. *Annals of the Rheumatic Diseases* [*Ann. rheum. Dis.*] **20**, 123–132, June, 1961. 6 figs., 44 refs.

Attention is drawn to the differing views on psoriatic arthritis as a clinical entity and to the reported negative response to the Rose–Waaler differential agglutination test (D.A.T.) and latex fixation test in psoriatic arthritis, as distinct from rheumatoid arthritis complicated by psoriasis and rheumatoid arthritis itself. At the General Infirmary at Leeds the author studied 157 patients with psoriasis and rheumatism. Of 121 with erosive arthritis, 91 were matched for age, sex, and duration of disease with 91 patients with uncomplicated arthritis in whom the response to the D.A.T. was positive. Radiographs were taken of the joints and the D.A.T. was carried out in both groups. A total of 18 patients in the psoriatic group giving a positive reaction to the D.A.T. were considered to have coincidental rheumatoid arthritis and were not included in the "psoriatic arthritis" group.

In radiographs of the hands and feet no significant difference was observed between the terminal interphalangeal joints of the thumbs and big toes in the psoriatic arthritis group and these joints in the rheumatoid group, but erosion of the proximal interphalangeal joints was commoner in psoriatic arthritis than in rheumatoid disease. In the distal joints of other fingers and toes erosions were seen more commonly in psoriatic than in rheumatoid disease, and when the erosions occurred in the fingers they were more severe. The terminal phalanges in psoriatic arthritis showed cystic changes and a characteristic whittling away of the bone, this last being seen only in association with nail changes. Erosive changes in the proximal interphalangeal joint and metacarpo- and metatarsophalangeal joints were commoner in rheumatoid arthritis than in psoriatic arthritis. The wrist was also more commonly affected in rheumatoid arthritis. Erosion of the ulnar styloid occurred in both groups and constituted a useful sign of disease. Erosion, sclerosis, and ankylosis of the sacro-iliac joints were seen more often in psoriatic than in rheumatoid arthritis.

Discussing these findings, the author considers it best to define psoriatic arthritis as an erosive arthritis in psoriatic patients giving a negative response to the D.A.T. The 18 cases of psoriasis and arthritis with a positive D.A.T. reaction differed little, clinically and radiologically, from cases of uncomplicated rheumatoid arthritis. Consequently it has been suggested by others that some patients with arthritis similar to rheumatoid arthritis and a negative D.A.T. reaction but without skin manifestations may be liable to develop psoriasis. Radiologically, the manifestations of psoriatic arthritis were more frequent in the distal interphalangeal joints. This arthritis was less severe both as regards joint involvement and osteoporosis than rheumatoid arthritis, and was characterized by erosion of the terminal phalanges and a higher incidence of sacro-iliac involvement. *J. S. Malpas*

1244. **The Nature of Anaemia in Rheumatoid Arthritis. V. Red Cell Survival Measured by Radioactive Chromium**
J. RICHMOND, W. R. M. ALEXANDER, J. L. POTTER, and J. J. R. DUTHIE. *Annals of the Rheumatic Diseases* [*Ann. rheum. Dis.*] **20**, 133–137, June, 1961. 2 figs., 14 refs.

In this paper from the University and the Northern General Hospital, Edinburgh, evidence is presented in support of the hypothesis that there is a mild haemolytic process in rheumatoid arthritis. The divergent results obtained with the Ashby technique and the method in which erythrocytes are labelled with radioactive chromium (^{51}Cr) are discussed. Using the ^{51}Cr method, Bunim in 1954 observed reduced survival of the patient's own cells and Weinstein in 1959 confirmed this finding. On the other hand, Lewis and Porter in a large series of patients later concluded that haemolysis was not a feature of rheumatoid arthritis.

In a group of 21 unselected patients with established rheumatoid arthritis but without clinical evidence of haemolytic disease or severe anaemia the survival time of the patient's own erythrocytes was measured by the ^{51}Cr technique of Mollison and Veall; in 6 of these the survival of compatible healthy donor cells was also estimated. In 5 healthy subjects determination of erythrocyte survival time showed that this was within normal limits by the method used.

There was no significant difference between the survival of the erythrocytes of patients with rheumatoid arthritis and that of normal subjects' own cells. "Comparison of the curves for cell survival between normal cells in patients with rheumatoid arthritis and own cells in normal subjects showed a difference which was highly significant" and indicated an increased rate of elimination in the rheumatoid patients. There was no apparent relationship between cell survival and the age and sex of the patients, clinical duration of disease, haemoglobin level, erythrocyte sedimentation rate, and the agglutination titre for sensitized sheep-cells.

In the authors' view the fact that cells from patients with rheumatoid arthritis survive normally in normal recipients indicates that the disorder is due to an extracorpuscular factor. Their findings also confirm those of Lewis and Porter that survival of own cells in rheumatoid arthritis is not significantly altered. However, the explanation of the increased rate of elimination of donor cells as compared with own cells might be, as Mollison has suggested, that a sample of cells from a patient having a random destructive process in the blood would contain more young cells and resistant cells than that from a healthy individual. The authors' observations conse-

quently lead to the conclusion that a mild haemolytic process is a factor in the production of the anaemia in rheumatoid arthritis. *J. S. Malpas*

1245. **Effects of Environmental Temperature upon Capillary Resistance in Patients with Rheumatoid Arthritis and Other Individuals**

J. L. POTTER and J. J. R. DUTHIE. *Annals of the Rheumatic Diseases* [*Ann. rheum. Dis.*] **20**, 144–148, June, 1961. 1 fig., 9 refs.

The first-named author, with Wigzell, had previously shown (*Ann. rheum. Dis.*, 1957, **16**, 357; *Abstr. Wld Med.*, 1958, **23**, 201) that the mean capillary resistance (C.R.) in patients with rheumatoid arthritis was significantly lower than in those with other disease. It was suggested that the C.R. may be a measure of some property of connective tissue, but the influence of environmental temperature was considered to be worth investigating. At the Northern General Hospital, Edinburgh, a total of 900 C.R. tests were performed on 72 subjects (41 patients with rheumatoid arthritis, 27 with other diseases, and 4 healthy subjects); rheumatoid arthritis was defined according to the criteria of the American Rheumatism Association. Patients were kept in bed during the investigation and most of the tests were carried out in the morning; those receiving steroid therapy were excluded from the general analysis of variance. The atmospheric temperature was recorded after each measurement of C.R. from a nearby mercury thermometer and additional data were obtained from the local meteorological station. Negative pressures were transmitted through a 23-mm. suction cup to the same area of skin (by aligning the outer rim of the cup with the biceps tendon and lowermost crease at the elbow) for 30 seconds; any petechiae appearing in the interval of 30 seconds following removal of the cup were counted.

There was no correlation between capillary resistance and barometric pressure, but there was a negative correlation between C.R. and environmental temperature in the rheumatoid group. The correlation between the two variables was positive in the other subjects. In the cases of rheumatoid arthritis treatment with corticosteroids tended to make the correlation between C.R. and temperature higher. It is concluded that these findings suggest a possible relationship between " rheumatism " and " weather ". *D. Preiskel*

1246. **A Controlled Trial of Phenylbutazone, Oxyphenbutazone, and a Placebo in the Treatment of Rheumatoid Arthritis**

R. I. MEANOCK and E. LEWIS-FANING. *Annals of the Rheumatic Diseases* [*Ann. rheum. Dis.*] **20**, 161–172, June, 1961. 13 refs.

Phenylbutazone (" butazolidin ") has in the past 10 years proved of value in the treatment of musculoskeletal disorders. A derivative of this drug, hydroxyphenylbutazone or oxyphenbutazone (" tanderil "), was the subject of the present trial carried out at the Royal Berkshire Hospital, Reading. Phenylbutazone, oxyphenbutazone, and a placebo were each given successively for 3 weeks to 60 patients (11 male and 49 female) with rheumatoid arthritis, each patient acting as his or her own control in a trial lasting 9 weeks. All had had the disease for at least one year, were not over 75 years of age, had a positive result in the sheep-cell agglutination test, and a raised erythrocyte sedimentation rate. Except for aspirin, no treatment was given for 2 weeks before the trial. The double-blind method of assessment was recorded on a standard form and included objective and subjective estimates.

Side-effects were reported by 28% of the patients while taking phenylbutazone, 31% while taking oxyphenbutazone, and by 31% while taking the placebo; altogether 11 patients were compelled to stop taking the tablets (3, 4, and 4 for each medicament respectively). It is concluded that there is little to choose between phenylbutazone and oxyphenbutazone in regard to relief of pain. The high incidence of side-effects attributed to the placebo was remarkable and tended to occur when this was the first treatment given. (The statistical methods employed are discussed in an appendix.)

D. Preiskel

1247. **The Significance of Percutaneous Liver Biopsy in Rheumatoid Arthritis.** (Zur Bedeutung der perkutanen Leberbiopsie bei der primär chronischen Polyarthritis) A. TAUBNER. *Zeitschrift für Rheumaforschung* [*Z. Rheumaforsch.*] **20**, 192–198, June, 1961. 3 figs., 16 refs.

In this study, reported from the General Hospital, Eilbek-Hamburg, of the liver changes in rheumatoid arthritis the thymol turbidity and Takata–Ara reactions were measured in 150 patients with confirmed rheumatoid arthritis. When the results of these investigations were abnormal the galactose tolerance test and "bromsulphalein" excretion tests were carried out. Liver biopsy was performed on the 33 patients in whom the bromsulphalein retention was greater than 5% or the thymol and Takata–Ara test results clearly abnormal, and the results in 29 are discussed.

Of these 29 biopsy specimens 11 were entirely normal, while 8 showed unimportant changes such as slightly increased amounts of fat, slight siderosis, or minimal brown atrophy. Of the 10 abnormal specimens 5 showed sinus leucocytosis, 7 swelling of the Kupffer cells, 3 siderosis, and 5 nuclear degeneration, while slight periportal infiltration, fatty change, and brown atrophy were each seen in one patient. The figures were too small for statistical assessment, but there was no definite relation between the results of liver function tests, including the bromsulphalein retention test, and the biopsy findings. The microscopical findings in 4 other patients were considered separately. Of these, 2 showed lobular and periportal infiltration and subcapsular necrosis which was regarded as secondary to peptic ulcer. In the 3rd patient atrophic cirrhosis was considered a fortuitous association, while in the 4th arthritis in one knee-joint was associated with pancreatitis and a hepatitis which progressed to cirrhosis and liver failure.

The author concludes that liver biopsy is useful in excluding liver disease in the presence of abnormal liver function tests in patients with rheumatoid arthritis and that cirrhosis due to liver damage by the rheumatoid process is extremely rare. *G. L. Asherson*

Physical Medicine

1248. **Lower Extremity Bracing in Cerebral Palsy**
R. V. FULDNER. *Cerebral Palsy Bulletin* [*Cerebral Palsy Bull.*] 3, 34–38, 1961. 2 figs., 13 refs.

The author reviews recent trends in the neurophysiological approach to the treatment of cerebral palsy and discusses current views on inhibition, facilitation, and integration. Control of balance for sitting and standing is often difficult for the child with cerebral palsy. Braces can help by inhibiting various aberrant movements, by facilitating stabilization, and by integrating associated movements. Bracing of the lower limbs will help with balance. He describes a type of brace which has proved durable, effective, and adaptable, and concludes with the reminder that bracing is an adjuvant to, and not a system of, treatment. *W. Tegner*

1249. **Electrodiagnosis in the Neuromuscular Disorders of Childhood.** [Review Article]
E. D. R. CAMPBELL. *Annals of Physical Medicine* [*Ann. phys. Med.*] 6, 80–88, May, 1961. 11 refs.

1250. **Quantitative Muscle Testing: Principles and Applications to Research and Clinical Services**
W. C. BEASLEY. *Archives of Physical Medicine and Rehabilitation* [*Arch. phys. Med.*] **42**, 398–425, June, 1961. 6 figs., 23 refs.

1251. **Effect of High-frequency Currents and Infra-red Rays on the Circulation of the Lower Limb in Man**
J. B. MILLARD. *Annals of Physical Medicine* [*Ann. phys. Med.*] 6, 45–66, May, 1961. 14 figs., 30 refs.

The author has investigated the effect of heat on circulation in the lower limb in man by injecting radioactive sodium (^{24}Na) into subcutaneous tissue or muscle and measuring the clearance rate with a scintillation counter. Superficial heating was effected by a luminous infra-red emittor and deep heating by short-wave diathermy. The areas studied were the skin of the thigh and the underlying muscle, the anterior tibial muscle, and the knee-joint, the same sites on the opposite leg being studied as a control in most cases. It was found that superficial heating increased the blood flow in the skin of the heated limb, but this did not increase the blood flow in proximal muscle, only distal muscle showing an increase in circulation. With deep heat more increase in the circulation in proximal muscle was demonstrated. But with both forms of heat the distal muscle showed a greater increase in circulation than did the proximal. Moreover, in both cases an increase in circulation in the distal muscles of the opposite limb was observed.

While heating may increase the blood flow in a limb by 100%, exercise increases the circulation much more. The author therefore suggests that the pain-relieving effect of heat must depend on factors other than increased blood flow, particularly as this does not occur in the proximal muscles of the heated limb. Superficial heating produces circulatory changes similar to those of deep heating and it is pointed out that superficial heating is cheaper than deep heating and may also be safer, as it has been shown that short-wave diathermy sometimes reduced the muscle blood flow temporarily.
W. Tegner

1252. **Changes in Blood Flow, Oxygen Uptake and Tissue Temperatures Produced by the Topical Application of Wet Heat**
D. I. ABRAMSON, R. E. MITCHELL, S. TUCK JR., Y. BELL, and A. M. ZAYAS. *Archives of Physical Medicine and Rehabilitation* [*Arch. phys. Med.*] **42**, 305–318, May, 1961. 4 figs., 18 refs.

Working at the University of Illinois College of Medicine, Chicago, the authors used a segment-type venous occlusion plethysmograph to measure blood flow in the forearm in 51 normal subjects. Blood from deep or superficial veins was collected for oxygen uptake measurements. Skin, subcutaneous, and muscle temperatures were recorded by thermocouples which were enclosed by the plethysmograph. The water temperature in the plethysmograph was 34° C. during initial measurements which were taken for 30 minutes. The temperature was then increased to 45° C., where it was maintained for 20 or 30 minutes, and then changed again to 34° C. Measurements were taken at 3- to 4-minute intervals and continued until control levels were reached. No generalized results were noted apart from occasional sweating.

The blood flow increased towards the end of the 30-minute heating period and then, after some delay, returned gradually to normal over an average of 54 minutes. The average total blood flow increase was 109·2 ml. per 100 ml. limb volume during heating and 130·6 ml. per 100 ml. after heating. In subjects heated for 20 minutes the increases were slightly less. The oxygen content of superficial venous blood fell slightly more than that of deep venous blood. The average total excess oxygen uptake of deep venous blood was 7·199 ml. per 100 ml. limb volume compared with 0·245 ml. per 100 ml. for superficial venous blood during heating. Control levels were reached in one hour. Skin temperature rose by an average of 6·4° C. from 34·7° C. The rise and fall were rapid. Subcutaneous temperature rose by an average of 5·4° C. from 34·6° C. Muscle temperature rose by an average of 1·8° C. from 35·8° C. These results are for 30 minutes' heating, the results for 20 minutes' heating being only a little less.

These results and those of other investigations are discussed at length, the conclusion being reached that wet heat is a potent agent in increasing local blood flow and tissue temperature, even in deep structures, and compares favourably with other, more elaborate, heating methods provided a high temperature (45° C.) is maintained for approximately 20 minutes. *J. B. Millard*

Neurology and Neurosurgery

1253. **Herpes Zoster and the Landry–Guillain–Barré Syndrome**

J. D. E. KNOX, R. LEVY, and J. A. SIMPSON. *Journal of Neurology, Neurosurgery and Psychiatry* [*J. Neurol. Neurosurg. Psychiat.*] **24**, 167–172, May, 1961. 1 fig., 31 refs.

Spread of the inflammatory lesion of herpes zoster to the spinal cord is a not uncommon complication of infection by the virus. The resulting clinical syndrome is commonly a focal flaccid paresis due to spread to the anterior horn cells or a spastic weakness and sensory impairment with a definite upper level suggesting involvement of the whole cord. More rarely the virus involves the brain itself, with disorders of consciousness, indicating a true encephalitis. These syndromes as a rule appear during the course of the initial illness. However, polyradiculitis occurring after a variable latent interval has been reported only 10 times in the world literature, and in this paper from the Northern General Hospital and Royal Infirmary, Edinburgh, the authors describe a further 3 cases in which this post-infective polyneuritis made its appearance some time after a classic infection with the virus of herpes zoster. Their first patient suffered from involvement of the upper limbs by the herpetic lesion, and one month later developed a motor polyneuritis which over the course of several weeks came to involve both legs as well as the upper limbs which were those initially involved. He was treated with corticosteroids, but died suddenly after exertion. The second patient suffered from a right-sided ophthalmic herpes and developed a motor polyneuritis some 6 weeks after this infection which spread from the lower limbs later to involve the upper limbs. The third patient suffered from a dorsal herpes and 2 months later developed polyneuritis and in the course of this a partial third-nerve palsy on the right.

All 3 cases were fully investigated, and abnormal nerve-conduction times confirmed the peripheral nature of the lesion. Cerebrospinal-fluid protein level was raised in 2 cases, with the albumino-cytological dissociation characteristic of the Landry–Guillain–Barré syndrome. All 3 cases were treated with corticosteroids, but the authors do not draw any conclusions from this small series as to the effect this treatment had upon the natural history of the disease. They make the point that the latent period between the herpes infection and the onset of the polyneuritis is inversely proportional to the severity of the syndrome. This conclusion they reach not only from their own cases, but from an appraisal of the 10 previously reported cases, which they list and describe in some detail. They discuss the possible pathogenesis of the polyradiculitis and draw an analogy between it and the commonly recognized post-exanthem cases of polyneuritis, suggesting an allergic or hypersensitivity phenomenon as its basis. *J. B. Foster*

1254. **The Treatment of Muscular Dystrophy with Nivaline in High Dosage.** (Il trattamento delle distrofie muscolari con dosi elevate di nivalina)

K. PERNOV, A. SAMARDJIEV, and V. NICOLKOV. *Cultura medica* [*Cultura med. (Roma)*] **21**, 149–164, March–April [received June], 1961. 4 figs., 25 refs.

Nivaline is a basic alkaloid extracted from the snowdrop *Galanthus nivalis* var. *gracilis*, which grows widely in Bulgaria. It is a reversible inhibitor of both true and pseudocholinesterase, and it thus has an action similar to that of neostigmine bromide. It has been widely used in Bulgaria and Russia in the treatment of many neuromuscular disorders, and the authors of the present report from the Institute for Psychoneurological Research, Sofia, describe the effects of this alkaloid in 30 cases of muscular dystrophy, which included 24 cases of progressive muscular dystrophy, 3 cases of spinal muscular atrophy, 2 cases of " neuromuscular atrophy ", and one case of myotonia congenita (Werdnig–Hoffmann syndrome).

Of 13 of the patients with muscular dystrophy given small doses of the alkaloid (up to 10 mg. a day) 5 showed no improvement, 7 minor improvement, and 1 definite improvement. The remaining 11 cases were given 25 mg. a day, with the result that 4 were markedly improved, 4 definitely improved, and the remaining 3 slightly improved. On this dosage one of the 3 patients with spinal muscular atrophy was also improved, but neither of the 2 with " neuromuscular atrophy ".

[While the authors provide general figures about age, sex, duration of illness, and other clinical features, they do not attempt to relate these to the clinical response, nor do they comment upon possible psychological, environmental (such as admission to hospital), and other factors that might have influenced the outcome of these tests. It is thus not easy to assess the significance of their findings.] *J. B. Cavanagh*

1255. **Thyroid Function and Myasthenia Gravis**

A. G. ENGEL. *Archives of Neurology* [*Arch. Neurol. (Chicago)*] **4**, 663–674, June, 1961. 3 figs., bibliography.

Thyroid function studies were carried out at the National Institute of Neurological Diseases and Blindness, Bethesda, Maryland, on 5 initially euthyroid patients with myasthenia gravis. Objective evaluation methods were used in assessment of the thyroid and the myasthenic status. It was found that hypermetabolism, however induced, made the myasthenia worse. In the absence of hypermetabolism neither suppression nor an increase in endogenous thyrotrophin secretion had any adverse effects on the myasthenia.

It is considered that this study does not confirm the existence of an inverse relationship between level of thyroid activity and the severity of myasthenia gravis.

Hugh Garland

DIAGNOSTIC METHODS

1256. **Subtentorial Tumors and Other Lesions: an Electroencephalographic Study of 121 Cases**

B. K. Bagchi, K. A. Kooi, B. T. Selving, and H. D. Calhoun. *Electroencephalography and Clinical Neurophysiology* [*Electroenceph. clin. Neurophysiol.*] **13**, 180–192, April, 1961. 4 figs., 32 refs.

The authors present from the Neuropsychiatric Institute, University of Michigan, Ann Arbor, the clinical, radiological, and electroencephalographic (EEG) findings in 121 patients with verified infratentorial lesions, of whom 113 had cerebral tumour. Definite EEG abnormalities were present in 100 cases (82·6%), and in 95 cases (78·5%) the EEG was interpreted as being characteristic of a deep-seated lesion. The factors regarded as characteristic were as follows: (1) anterior, posterior, or diffuse bilaterally synchronous bursts of delta, theta, or alpha activity; (2) shifting interhemispheric bursts between homologous regions; (3) parasagittal bianterior-biposterior variability; (4) parasagittal lateral variability; (5) over-all unihemispheric emphasis of decrease in wave length or increase in voltage; and (6) antero-posterior genuine phase difference. Although these features occur in many conditions other than space-occupying lesions—for instance, in epilepsy and inflammatory, traumatic, and degenerative cerebral disease—the EEG findings may be very helpful when the history excludes these conditions.

The EEG abnormalities were more evident contralateral to the site of the tumour and this observation was shown to be statistically significant; notably it was particularly evident in cases without any rise in intracranial pressure. Asymmetry with a contralateral predominance of abnormalities occurred in 73% of cases with lateralized infratentorial lesions. On the other hand, a number of patients with a mid-line tumour also showed asymmetrical EEG tracings. *L. G. Kiloh*

1257. **Electro-clinical Profile of 117 Deep Cerebral Tumors**

J. G. Small, B. K. Bagchi, and K. A. Kooi. *Electroencephalography and Clinical Neurophysiology* [*Electroenceph. clin. Neurophysiol.*] **13**, 193–207, April, 1961. 6 figs., bibliography.

At the Neuropsychiatric Institute, University of Michigan, Ann Arbor, 117 patients with verified cerebral tumour at least 2 cm. in depth from the cerebral cortex were studied, all those with temporal-lobe or infratentorial tumours being excluded. Electroencephalograms (EEGs) were recorded by means of an elaborate system of 26 montages. The following features were regarded as providing some indication of a deeply situated tumour. (1) Synchronous bi-anterior or bipolar bursts of delta, theta, or alpha activity; (2) shifting bursts between homologous anterior or posterior areas of the two hemispheres; (3) the asynchronous appearance of parasagittal bursts either antero-posteriorly or laterally; (4) a predominance over one hemisphere of episodes of increased amplitude or of increased frequency of the bilaterally synchronous or shifting bursts; and (5) a slow background record. "Bursts" were defined as activity occurring in sudden episodes of any wave length with an amplitude 50% greater than that of the background. Similar findings may also occur in traumatic, vascular, and post-traumatic conditions and also in metabolic and other cerebral disorders, but they are helpful in differentiating deep from superficial tumours.

The EEG suggested a deep situation of the tumour in 85 of the 177 cases. In 18 cases the "depth signs" were obscured by prominent unilateral slow wave foci leading to the erroneous diagnosis of a superficial lesion. It is suggested that two fundamental mechanisms, variably interlocked, are concerned in the production of the EEG abnormalities described: (1) neuronal transmission to the cortex of abnormal potential changes in the deep nuclear masses irritated by the tumour, and (2) direct interference with cortical function from below resulting from the impaired circulation and attendant oedema caused by the presence of a deep tumour. Other factors such as raised intracranial pressure and tentorial herniation play a part in some cases, but marked EEG abnormalities frequently occur in their absence. In this series it was noted that meningiomata of the olfactory groove were more prone to give rise to bi-anterior delta activity than intrasellar or chiasmal tumours. In no case of thalamic tumour was the EEG normal. Although theta discharges did occur in some cases, no support was found in this study for the frequently expressed view that in the presence of a cerebral tumour theta activity suggests a deep situation of the lesion. *L. G. Kiloh*

1258. **An Electroencephalographic Study of the Analeptic Effects of Imipramine**

L. G. Kiloh, K. Davison, and J. W. Osselton. *Electroencephalography and Clinical Neurophysiology* [*Electroenceph. clin. Neurophysiol.*] **13**, 216–223, April, 1961. 6 figs., 33 refs.

There have been several reports in the literature that when imipramine ("tofranil") is taken in large quantities (800 mg. or more) in suicidal attempts attacks of grand mal commonly occur. When the drug is given in therapeutic doses to epileptics there may occasionally be some increase in the frequency of their attacks, while grand mal may occur, though rarely, as a side-effect of the drug in non-epileptic subjects under treatment for depressive states. In this study, reported from the University of Durham, electroencephalograms (EEGs) were obtained from 24 non-epileptic subjects and 36 epileptics before, during, and after the slow intravenous infusion of 75 mg. of imipramine; all but 2 of the epileptics suffered from cortical epilepsy.

In the non-epileptic group EEG changes were slight; thus diffuse theta activity appeared in 8 and in the majority there was some reduction in the amount of alpha activity. All the epileptic patients had undergone EEG studies. In 16 of them these had failed to reveal any epileptiform discharges, but after the infusion of imipramine such discharges appeared in 3 cases. Again, of 14 patients in whom EEG confirmation of the diagnosis had already been obtained but in whom a 10-minute EEG recording before injection of the drug lacked any

epileptiform features, such features appeared in 11 as the result of the drug administration. In 4 of 6 cases with epileptiform features evident before the injection there was a significant increase in their incidence. Of the 18 cases in which EEG activation occurred, a localized focal sharp wave focus appeared in 4 and bilateral spike and slow wave discharges in 12. There was a considerable increase in the incidence of epileptiform discharges in the 2 cases of centrencephalic epilepsy included in the series.

In 21 of the epileptic subjects activation with bemegride given at the rate of 5 mg. every 15 seconds, following an initial dose of 5 mg. per 10 kg. body weight, was attempted. This was successful in 10 cases; of the same group, 9 had responded to imipramine. In 2 out of 7 patients activated by both drugs imipramine gave rise to a focal discharge, whereas bemegride caused a bilateral abnormality. Side-effects, notably vertigo, nausea, and vomiting, were frequent following imipramine and hypotensive collapse occurred in 4 patients. It is concluded that as an activating agent of the EEG in epileptics imipramine appears to be as effective as bemegride and may be more likely to provoke focal discharges.

L. G. Kiloh

BRAIN AND MENINGES

1259. Cerebral Infarction

A. B. CARTER. *Geriatrics* [*Geriatrics*] **16**, 278–299, June, 1961. 2 figs., 29 refs.

In this survey of 510 consecutive patients under 80 years of age suffering from cerebral infarction and admitted to Ashford Hospital, Middlesex, in the 7-year period 1952 to 1958 the author summarizes current views on the aetiology and definition of this condition and gives an account of its local incidence and distribution. He takes the view that cerebral vascular insufficiency is quite commonly the cause of intracerebral infarction. Considerable emphasis is laid on the differential diagnosis, especially as between cerebral embolism, cerebral thrombosis, and intracerebral haematoma. He endeavours to assess various forms of "immediate" therapy, including vasodilatation and the administration of anticoagulants. He considers that anticoagulant drugs are of benefit in the immediate treatment of cerebral embolism and of slow ingravescent cerebral thrombosis (with progressive cerebral infarction), but comes to the conclusion that no other form of cerebral infarction is subsequently influenced by these or any other measures. [By ingravescent cerebral thrombosis he means infarction giving rise to increasing paralysis over 2 or more hours.] He also notes that the best results were obtained in patients who were not unconscious and whose lesions were incomplete when treatment was begun. Finally he discusses some of the indications for, the contraindications to, and dangers of anticoagulant therapy in the treatment of cerebral infarction.

[Not all will agree with the author concerning the improvement to be expected from the use of anticoagulant drugs in ingravescent cerebral infarction. Indeed, some will consider that there is virtually no place for these drugs in cerebral infarction from any cause, because of the impossibility of ascertaining that cause with certainty and also because of the complications which may ensue during anticoagulant treatment following cerebral infarction whatever its cause.] *P. D. Bedford*

1260. Cerebral Infarction and Hypertension

T. LOW-BEER and D. PHEAR. *Lancet* [*Lancet*] **1**, 1303–1305, June 17, 1961. 3 figs., 15 refs.

The authors studied the records of 109 patients who had been treated at the Middlesex and Central Middlesex Hospitals, London, in the periods 1933–59 and 1953–60 respectively and showed necropsy evidence of cerebral infarction. Blood-pressure readings recorded close to the time of the stroke were available, and these were corrected for age and sex by the method of Hamilton *et al.* (*Clin. Sci.*, 1954, **13**, 11, 37). Three groups of cases were considered: those in which the infarction was thought to have been precipitated by a factor such as operation, haemorrhage, or myocardial infarction; those with uncomplicated infarctions; and those in which the infarction was accompanied by diabetes. Adequate records were available in 19 of the 37 cases of the first group of complicated infarctions, and in these there was a mean fall in blood pressure at the time of the stroke from about 190/100 mm. to 140/80 mm. Hg. The mean blood pressure in the 62 non-diabetic uncomplicated cases was 207/115 mm. Hg, and this is compared with figures given by Hamilton *et al.* for healthy men and women aged 60 of 145/80 and 155/90 mm. Hg respectively. The blood pressure in the 10 diabetic cases did not differ from that in the non-diabetic uncomplicated cases.

In a series of patients with myocardial infarction reported from the U.S.A. by Sigler (*Ann. intern. Med.*, 1955, **42**, 369; *Abstr. Wld Med.*, 1955, **18**, 130) the blood-pressure levels were distinctly lower than those found in the present series of cases of cerebral infarction. For this and other reasons the authors believe that hypertension is often associated with cerebral infarction and that cerebral arterial disease differs in many ways from coronary arterial disease.

[To compare observations obtained in this way with data from another country obtained by quite different methods seems to the abstracter to be of at least questionable validity.] *Bernard Isaacs*

1261. Thrombolysis with Fibrinolysin in Cerebral Arterial Occlusion

B. J. SUSSMAN and T. S. P. FITCH. *Angiology* [*Angiology*] **12**, 169–173, May, 1961. 3 figs., 2 refs.

Fibrinolysin was given in the treatment of 11 patients with cerebral or carotid occlusion as demonstrated angiographically. The enzyme was administered by the intracarotid route, angiography being repeated after treatment. In 5 patients with middle cerebral occlusion, 3 of whom had sustained occlusion in the course of auricular fibrillation, there was evidence of restitution of the lumen. Partial clearing was observed in 2 patients with carotid thrombosis. In the remaining 4 cases of middle or anterior cerebral occlusion no significant changes were noted.

There were 7 deaths, 4 of these occurring in the patients with vascular clearing. At necropsy in 3 cases showing clearing of middle cerebral occlusion there was no evidence of any haemorrhagic change. The authors point out that cerebral ischaemia can proceed to encephalomalacia within a very short time; they therefore emphasize the importance of treating these cases as quickly as possible after symptoms have developed. Apart from speed, hypothermia may be another important adjuvant of treatment.

In this series of cases angiography was carried out immediately after clinical assessment of the patient's condition. This was followed by intracarotid injection of 200,000 to 300,000 units of fibrinolysin over a 20-minute period. This route was selected because it allows a rapid concentration of the enzyme at the site of occlusion and it is immediately available at the time of angiography. *A. S. Douglas*

1262. **Evaluation of Controlled Digital Carotid Artery Compression in Cerebrovascular Insufficiency: Carotid Sinus (Cardioinhibitory Type) Response**
W. J. FRIEDLANDER. *Neurology* [*Neurology (Minneap.)*] **11**, 503–514, June, 1961. 1 fig., 40 refs.

The author of this paper from the National Veterans Epilepsy Center and the Veterans Administration Hospital, Boston, has studied the effect of compression of the carotid artery and the sensitivity of the carotid sinus in patients with cerebrovascular insufficiency. It has been reported that a hypersensitive carotid sinus occurs most frequently in old people and in patients suffering from cerebrovascular disease. The technique of digital compression of the carotid artery in a series of 479 patients (aged under 20 to over 80 years) is described. From this number 446 were selected in whom there was definite clinical evidence of the presence or absence of cerebrovascular insufficiency and the insufficiency, when present, could be related to one particular arterial system. The electroencephalogram (EEG) in all the patients was sufficiently free from artefact to be reliably interpreted. Of the 446 patients, 280 had no cerebrovascular disease and 166 patients had localized disease. An abnormal carotid sinux reflex is defined as one in which the pulse rate is reduced to at least one-half of the pre-compression rate. Patients giving this vagal response received atropine subcutaneously, and the test was repeated in order to establish that the ischaemic effects of carotid occlusion were not responsible for the slowing, the EEG tracing being used as the diagnostic criterion.

The author concludes that in patients under the age of 60 increased carotid sinus sensitivity occurs significantly more often in the presence of cerebrovascular insufficiency. A possible explanation is that the brain damage occasioned by the ischaemia alters the carotid sinus reflex itself, but this hypothesis is difficult to support. Alternatively, commonly associated atheroma at the bifurcation and cerebrovascular insufficiency may directly and locally involve the carotid sinus area, either by local distortion of the nerve endings or by allowing the more rigid artery to be more easily affected by mechanical pressure. In patients over the age of 60 there was little difference between those with and those without evidence of cerebrovascular insufficiency in the sensitivity of the carotid sinus, and the author suggests that its use as a diagnostic sign should be limited to patients in the younger age group. There was no evidence in this study that the hypersensitive carotid sinus plays any part in the transient ischaemic episodes commonly recognized in patients suffering from cerebrovascular insufficiency.
J. B. Foster

1263. **Observations on the Carotid Bruit**
W. B. MATTHEWS. *Journal of Neurology, Neurosurgery and Psychiatry* [*J. Neurol. Neurosurg. Psychiat.*] **24**, 161–166, May, 1961. 13 figs., 2 refs.

The author of this paper from the Derbyshire Royal Infirmary questions the view that a systolic bruit in the neck is reliable evidence of carotid stenosis, and he supports his argument with the clinical, phonocardiographic, and arteriographic records of 5 patients. In 2 patients a systolic bruit in the neck accompanied complete occlusion of the internal carotid artery and narrowing of the origin of the external carotid. The third patient had bruits on both sides, accompanied by stenosis of the common, external, and internal carotid arteries on the left and occlusion of the internal carotid and stenosis of the external carotid arteries on the right. The fourth patient had a loud bruit on the left side associated with stenosis of the right internal carotid artery with no bruit, but a bruit was heard on the right after an operation for disobliteration of this vessel. In the fifth patient, a woman of 36 who had sustained a subarachnoid haemorrhage from a carotid aneurysm, a bruit first appeared after incomplete ligation of the common carotid artery on the affected side. This disappeared after ligation of the internal carotid artery, but reappeared a few days later on the opposite side. In this case the cause of the bruit was thought to be increased blood flow through collateral channels.

It is concluded that there is no simple relationship between stenosis of the internal carotid artery and a systolic arterial bruit, and that angiography is necessary for the accurate diagnosis of occlusive carotid artery disease. *Bernard Isaacs*

1264. **The Clinical Features of Cranio-vertebral Tumours**
(К клинике краниовертебральных опухолей)
D. K. BOGORODINSKIJ and G. P. SUVOROV. *Журнал Невропатологии и Психиатрии* [*Ž. Nevropat. Psihiat.*] **61**, 497–500, No. 4, 1961. 1 fig., 9 refs.

Cranio-vertebral tumours may be divided into three topographical varieties: (1) extramedullary tumours arising at the level of the junction of the skull and vertebral column; (2) intramedullary tumours at the same level; and (3) tumours arising in the rhombencephalon and protruding through the occipital foramen into the spinal canal. These again are usually subdivided into cerebello-spinal or bulbo-spinal according to the site of their origin. The authors have studied these tumours since 1945, basing their investigations on 2 personal cases and 29 case histories collected from the literature. The majority of these tumours were of neuro-

ectodermal origin (especially ependymomata) and only a few of mesodermal origin (chiefly vascular). Clinically they are characterized by the early onset of signs of hypertension and hydrocephalus, manifested by headache, vomiting, and papilloedema; later, static disturbances, ataxia of cerebellar type, diplopia, nystagmus, failing sight, rigidity in the neck and occipital region and increased sensitivity of the nape of the neck to palpation. In 2 cases early bulbar symptoms (dysphagia or dysarthria) were observed. In some cases the pyramidal tracts were implicated, and in others there were signs of deep sensory loss in the limbs, especially the arms. The voice may become nasal owing to involvement of the glossopharyngeal nerve.

Full clinical details are given of one case in a man aged 48 in whom symptoms had first appeared 11 years previously. Operation revealed an ependymoma of the 4th ventricle extending through the occipital foramen down to the second vertebra. This was resected, with subsequent relief of all symptoms except slight nasal intonation, some deviation of the tongue to the right, and hyperaesthesia of the skin corresponding to the upper two cervical dermatomes. The deep reflexes in the right arm remained diminished. *L. Firman-Edwards*

1265. **Changes in the Brain Potentials in Tumours of the Lateral Ventricle.** (Изменения мозговых потенциалов при опухолях в районе боковых желудочков)
D. G. Šmel'kin. *Журнал Невропатологии и Психиатрии* [*Ž. Nevropat. Psihiat.*] **61**, 522–527, No. 4, 1961. 4 figs., 12 refs.

Tumours in the region of the lateral ventricles usually present a meagre and non-characteristic symptomatology, which makes early diagnosis difficult. The author has carried out an electroencephalographic (EEG) investigation of 18 cases of such tumours and presents his findings, together with 3 case histories in detail, as well as the history and EEG findings in a case of medulloblastoma involving the optic chiasma and both thalami for comparison. Of the 18 lateral-ventricle lesions, 16 were tumours of various types, one was a cyst, and one a hydatid of cysticercosis in the right lateral ventricle; 14 of them were unilateral (7 on the left side and 7 on the right) and 4 bilateral, while 3 were confined to the anterior horn, 5 to the inferior horn, and one to the posterior horn. Two of the patients were children aged 9 years, but all the others were adults.

The EEGs, for which bipolar leads were employed, showed that in 12 cases alpha rhythm was weak or suppressed on the affected side, in 2 it was absent on both sides, and in 4 it was symmetrical; in lesions involving the anterior horn alone alpha rhythm was little affected, whereas in those involving the inferior horn it was either absent or disorganized. Beta rhythm was asymmetrical in 2 cases; the most characteristic finding was the appearance of slow waves (1 or 2 per second) of large amplitude (150 to 200 mV.) in the leads near to the lesion on the affected side. Theta waves at 4 to 7 per second, which are often observed in tumours of the third ventricle and occipital fossa and were clearly marked in the case of thalamic medulloblastoma described for comparison, were conspicuous by their absence in the EEGs of these patients with lateral-ventricle tumours. These oscillations are probably associated with involvement of the diencephalon. *L. Firman-Edwards*

1266. **Outbursts of Rage and Pathological Sleep Due to an Anterior Midline Tumour.** (Wutverhalten und pathologischer Schlaf bei Tumor de vorderen Mittellinie)
K. Poeck and G. Pilleri. *Archiv für Psychiatrie und Nervenkrankheiten* [*Arch. Psychiat. Nervenkr.*] **201**, 593–604, 1961. 2 figs., 36 refs.

A case is reported showing at first unprovoked outbursts of rage, comparable to the " sham rage " of animal experiments, and later pathological sleep. The patient could be roused easily, but would go back to sleep as soon as stimulation ceased. Post-mortem examination showed an oligodendroglioma which had originated in structures belonging to the limbic system and had subsequently invaded the anterior thalamus (the nonspecific thalamic system). The authors discuss these findings in the light of various neurophysiological theories regarding the neuronal organization of affect and sleep.—[From the authors' summary.]

1267. **What is Arrested Hydrocephalus?**
R. W. Schick and D. D. Matson. *Journal of Pediatrics* [*J. Pediat.*] **58**, 791–799, June, 1961. 9 figs., 13 refs.

Working in the Department of Neurosurgery of the Children's Hospital Medical Center, Boston, the authors set themselves the task of defining the indications for, and limitations of, surgical treatment of early or mild hydrocephalus and of evaluating the results of such treatment. This naturally led to an attempt to define what is meant by " arrested " hydrocephalus, from which the authors concluded that it is not justifiable to consider the hydrocephalus to be arrested and optimum treatment achieved if the rate of growth of the head continues steadily in parallel with, but still above, the normal growth curve. As they state, " in a young infant, an already enlarged head should not continue to grow at all until the body size has caught up to the head size and each then proceeds within its normal range ".

In order to arrive at a more precise definition of " arrested " hydrocephalus the authors have studied the pattern of head growth of 40 hydrocephalic patients all of whom had been subjected to at least one of the various shunting procedures, but none had associated meningomyelocele. Following successful operation the head circumference first diminished by 1 to 2 cm. and then either remained stationary or grew very slowly until sufficient time had elapsed for the size of the head to occupy its normal place at or below the normal ninetieth percentile growth curve. In contrast, serial measurements in 8 out of 20 infants who were thought to have " arrested " hydrocephalus (and who had not been operated on) showed continued slow head growth. This was taken as an indication for a shunting procedure, the performance of which led first to reduction in, and then arrest of, head growth. The finding of a normal intracranial pressure in these cases tended to obscure the

presence of progressive hydrocephalus, while the apparently relatively normal developmental progress of these infants engendered a false sense of security and delayed the date of operation.

In their discussion the authors contend that it is necessary to diagnose and treat hydrocephalus as early as possible in order to minimize the risk of brain damage. The sequelae of chronic mildly increased intracranial pressure during early life may not appear for several years. Developmental progress then stops with discouraging frequency at a subnormal intellectual level. It is considered that complete spontaneous arrest of hydrocephalus in infants under 2 years of age (excluding cases associated with meningomyelocele) is extremely rare. The authors are highly [and justly] critical of the report by Laurence (*Lancet*, 1958, **2**, 1152; *Abstr. Wld Med.*, 1959, **25**, 361) who claimed to have found a high proportion (46%) of cases of spontaneous arrest of the hydrocephalus in infants who survived the first 3 months of life.

[The abstracter would agree about the rarity of spontaneous arrest, but considers that the authors' recommendation of surgical treatment for all mild cases is on less certain grounds. Early success is often followed by very late operative complications which may offset the initial advantages gained.] *John Lorber*

1268. **Electro-clinical Correlations in Childhood Epilepsy**
E. J. A. NUFFIELD. *Epilepsia* [*Epilepsia* (*Boston*)] **2**, 178–196, June, 1961. 3 figs., 23 refs.

This paper from the Maudsley Hospital, London, considers the relationship of clinical seizure patterns and electroencephalographic (EEG) findings in a group of 322 epileptic children. Uniformity in seizure pattern is less common (70%) than uniformity of the electrical pattern (91%). An EEG record specific for epilepsy was obtained in 79% of patients, and it was possible to divide the records into two groups: (1) those in which discharges appeared to arise from a cortical focus, and (2) those where the discharge arose from subcortical structures. The EEG classification gave a clearer insight into the underlying physiological disturbances than did the clinical fit pattern, although certain fairly close correlations of fit and EEG patterns did emerge—for example, the 3-cycles-per-second spike-and-wave record with petit-mal attacks. The author has demonstrated the correlation between the EEG disturbance and interictal behaviour disturbance of aggressive or neurotic type, which is greater than that between behaviour and clinical seizure pattern. *J. B. Stanton*

1269. **The Effect of the Removal of the Nucleus Dentatus on the Parkinsonian Syndrome**
S. TÓTH. *Journal of Neurology, Neurosurgery and Psychiatry* [*J. Neurol. Neurosurg. Psychiat.*] **24**, 143–147, May, 1961. 3 figs., 19 refs.

Writing from the Institute of Neurosurgery, Budapest, the author describes the effect in 3 patients of unilateral ablation of the dentate nucleus of the cerebellum. In each case a posterior fossa approach was made and the dentate nucleus with surrounding white matter was removed by suction. All 3 patients were suffering from a Parkinsonian syndrome, which in 2 of them was post-encephalitic. The author does not propose this procedure as a method of treatment of Parkinsonism, but he does draw certain conclusions between the relationship of Parkinsonian tremor, rigidity, and hypokinesis and the tremor and hypotonia of cerebellar disorders. The effect of ablation was to render the ipsilateral limbs hypotonic; this defect was permanent and was most marked in one of these patients who had already been subjected to pallido-thalamotomy. The effect of the ablation was markedly to reduce the tremor in 2 cases and this reduction was, according to the author, prolonged into the convalescent phase so that 2½ years after operation the patients were continuing to show improvement. Ablation of the dentate nucleus did not affect the hypokinesis of the Parkinsonian state in any of the 3 cases.

[The abstracter had some difficulty in interpreting the criteria of improvement and in appreciating exactly to what extent the 3 patients had been benefited by this surgical procedure.] *J. B. Foster*

1270. **Methyl Phenidate in Parkinsonism**
A. M. HALLIDAY and P. W. NATHAN. *British Medical Journal* [*Brit. med. J.*] **1**, 1652–1655, June 10, 1961. 1 fig., 3 refs.

The fact that methyl phenidate (" ritalin ") will relieve the Parkinsonian state induced by reserpine and also reduce surgically induced tremor in animals has prompted the authors, at the National Hospital, Queen Square, London, to try the effect of this drug in cases of Parkinsonism. In a pilot investigation on 4 male patients with this disease intravenous injection of the drug caused a striking reduction in rigidity and improvement in mood and speech disturbance. Following this 12 patients were given the drug by mouth in an extended double-blind trial with or without continuation of their previous medication. Oral administration was found to be less effective. Half the patients felt better during the treatment, though some of the beneficial effect was not due to any specific anti-Parkinsonian action. Freedom of movement was increased and tremor and rigidity were reduced in some patients, and in one severely affected patient improvement in dysarthria occurred. One-quarter of the patients tested were no better and one-quarter felt worse. *R. Wyburn-Mason*

1271. **Exacerbations in Parkinsonism**
M. E. GRANGER. *Neurology* [*Neurology* (*Minneap.*)] **11**, 538–545, June, 1961. 30 refs.

It is generally believed that the Parkinsonian state tends to run a slowly progressive downhill course, but in this paper from the Royal Infirmary, Cardiff, the author draws attention to the little-recognized fact that exacerbations of the disease are not uncommon, and discusses the causes of such exacerbations. The effects of abrupt drug withdrawal in a series of 20 cases and, in a personal series of 109 cases, of stress, of alcohol, and of other drugs not being given principally for the Parkinsonian state are discussed at length. *J. B. Foster*

Psychiatry

1272. **Delirium Tremens. A Comparative Study of Pathogenesis, Course, and Prognosis with Delirium Tremens.** [In English]
G. LUNDQUIST. *Acta psychiatrica et neurologica Scandinavica* [*Acta psychiat. scand.*] **36**, 443–466, 1961. 1 fig., 34 refs.

An analysis is presented of the case histories of 74 male patients with delirium tremens (deliriants) admitted to Långbro Hospital, Stockholm, over a period of 4½ years, the findings being compared with those in a group of 74 patients admitted for alcoholism without delirium tremens. Various factors contributing to alcoholism were investigated in an attempt to determine those which distinguished the two groups. Of the deliriants, 60% had consumed large quantities exclusively of strong liquor during the 4 weeks preceding admission, compared with only 32% of the alcoholics without delirium. Neurosis and psychopathy were present in 23% of the deliriants and in 65% of the alcoholics. The incidence of mental illness and abnormality was about five times higher in the parents and siblings of the alcoholics without delirium than in those of the deliriants. Abstinence from alcohol appeared to be a precipitating factor in about a quarter of the cases of delirium tremens. Clear-cut enzyme disturbances were demonstrated in the deliriants, the serum glutamic–oxalacetic transaminase level being significantly increased in 90% (probably indicating acute liver damage) compared with 20% of the alcoholics without delirium. The mortality was about 10% during the course of the first attack of delirium tremens, and of those patients who survived, about 40% had one or more further attacks. Of the survivors, 30% "more or less" deteriorated, compared with 22% of the alcoholics without delirium.

J. B. Stanton

1273. **Some Psychiatric Consequences of Gastrectomy**
F. A. WHITLOCK. *British Medical Journal* [*Brit. med. J.*] **1**, 1560–1564, June 3, 1961. 12 refs.

The chance observation of alcoholism following partial gastrectomy led the author of this paper from Newcastle General Hospital to study the long-term psychiatric sequelae of this operation in 25 patients (17 male and 8 female) who were admitted to a psychiatric ward at some stage following partial gastrectomy for duodenal (22 cases) or gastric ulcer (3). Of the 17 male patients, 9 were admitted for alcoholism, 2 for drug addiction, and 6 for an anxiety-depressive syndrome. Of the 8 female patients, 3 were drug addicts and 5 had anxiety-depressive symptoms. Those patients with addiction tended to take the alcohol or drugs because of troublesome "dumping" symptoms.

The association between gastrectomy and addiction to alcohol or drugs is considered to be one of cause and effect. Nevertheless, the possibility of such a complication occurring in a particular individual is not necessarily an absolute contraindication to operation. It is suggested, however, that the preoperative discovery of psychopathic or alcoholic tendencies in a patient should lead to psychiatric care both before and after the operation. An association between gastrectomy and subsequent psychoneurosis is less clear cut. In such cases the operation probably functions as a non-specific stress in a previously vulnerable individual.

A. Balfour Sclare

1274. **Learning and Recall under Hypnosis and in the Wake State: a Comparison**
J. P. DAS. *Archives of General Psychiatry* [*Arch. gen. Psychiat.*] **4**, 517–521, May, 1961. 1 fig., 14 refs.

This paper from Utkal University, Cuttack, India, tries to settle the controversy regarding the effects of hypnosis on learning and recall. There are 3 theories about recall—that it is better, worse, or no different in the hypnotic as compared with the waking state. These correspond to 3 broad concepts of hypnosis itself: (1) the production of an over-all increment in abilities; (2) a general deterioration of abilities due to cortical inhibition in the Pavlovian sense; (3) a state of suggestibility not differing essentially from waking suggestibility. Previous work is reviewed, and the major pitfalls enumerated; these, which were obviated in the present study, are: controlling the depth of hypnosis, meaningfulness of material used for testing, cues provided by the hypnotist and the experimental design, and the attitude of the subject.

Six psychology students took part in the study, all capable of reaching the stage of somnambulism, this being tested for by positive and negative hallucinations and post-hypnotic amnesia. Three sessions were given to each subject: (1) waking learning and hypnotic recall; (2) hypnotic learning and waking recall; and (3) waking learning and waking recall. Paired associate words from a Word Association Test were used as the material. The true purpose of the tests was not known to the subjects, and recall in the hypnotic sessions was obtained by asking for associations to one of the word pairs; by these means cues were avoided. In the final session in the waking state ordinary recall was used. The first 3 subjects learned lists A, B, and C and had sessions 1, 2, and 3 in that order, while the other 3 subjects learned lists C, B, and A in that order, and had session 2 first, then 1, and finally 3.

Results showed that, of the 3 recall scores, the waking recall of material learned under hypnosis was the lowest; that learning of meaningful material under hypnosis is neither superior nor inferior to learning in the waking state; and that no permissible conclusions can be drawn in regard to the lower recall scores under hypnosis as compared with recall scores in the waking state. But it is pointed out that retention rather than learning is

weakened by sedatives, and the results of the present study would confirm this if hypnosis is regarded as a state of cortical inhibition. *F. E. Kenyon*

1275. **Evoked Cortical Potentials and Sensation in Man**
C. SHAGASS and M. SCHWARTZ. *Journal of Neuropsychiatry* [*J. Neuropsychiat.*] **2**, 262–270, June, 1961. 10 figs., 11 refs.

This paper from the State University of Iowa, Iowa City, describes initial experiments with a new psychophysiological method based on the measurement of cortical potentials evoked by sensory stimulation, both visual and electrocutaneous, and recorded from scalp electrodes. These potentials, which were first demonstrated by Dawson in 1947 (*J. Neurol. Neurosurg. Psychiat.*, **10**, 134) but are difficult or impossible to detect in the ordinary electroencephalogram, consist of an initial primary response of brief latency and duration, followed by several secondary waves which may continue for longer periods and are more variable. It was found that these secondary waves were influenced by psychological factors, for example, the subject's mood or his performance of mental arithmetic. The first sign of a primary response occurred at the sensory threshold; sub-threshold stimuli provoked no cortical response, suggesting that the evoked potential may be an objective sign of sensory awareness.

The authors describe the methods used and present a number of examples of the records obtained. They consider that it will be possible by this method to study the psychological correlates of directly measurable states of cortical excitability and envisage that such studies offer intriguing possibilities. *B. M. Davies*

PSYCHONEUROSIS

1276. **A Controlled Trial of Methaminodiazepoxide (Chlordiazepoxide, " Librium ") in the Treatment of Anxiety in Neurotic Patients**
F. A. JENNER, R. J. KERRY, and D. PARKIN. *Journal of Mental Science* [*J. ment. Sci.*] **107**, 575–582, May [received July], 1961. 7 refs.

A double-blind cross-over trial of chlordiazepoxide and a placebo in 95 neurotic patients suffering from anxiety is described in this paper from the United Sheffield Hospitals. The drug was significantly active in relieving symptoms associated with anxiety over a 2-week period, 58 of the 95 patients describing its effect compared with that of the placebo as " good " or " very good ". The action appeared to be rapid, and in patients who relapsed when the placebo was substituted the relapse was also rapid. The response was most marked in patients suffering from phobias or somatic symptoms, and less marked in hysterical patients. Only two side-effects, drowsiness and ataxia, were definitely attributable to chlordiazepoxide; 23 patients complained of drowsiness during the first 2 or 3 days of treatment, but this passed off, and 8 complained of ataxia, in 2 of whom it was observed objectively. The dosage of the drug was reduced in 2 cases and the ataxia became less severe. It is pointed out that no long-term treatment was given and only symptomatic relief was assessed. *E. H. Johnson*

1277. **A Controlled Comparison of Methaminodiazepoxide (Chlordiazepoxide, " Librium ") and Amylobarbitone in the Treatment of Anxiety in Neurotic Patients**
F. A. JENNER, R. J. KERRY, and D. PARKIN. *Journal of Mental Science* [*J. ment. Sci.*] **107**, 583–589, May [received July], 1961. 6 refs.

In a further investigation of the value of chlordiazepoxide in the treatment of anxiety in neurotic patients [see Abstract 1276], the action of the drug was compared with that of amylobarbitone, a double-blind technique being used. A group of 92 patients received each drug for a fortnight, the dosage of chlordiazepoxide being 20 mg. 3 times a day and that of amylobarbitone 60 mg. 3 times a day. A significant majority of the patients (59) preferred chlordiazepoxide. The authors state that it was difficult to assess the specificity of the drug for particular symptoms, since patients feeling better usually found improvement in all symptoms. Ataxia was not a side-effect in this series. An attempt was made to compare the effect of chlordiazepoxide in various types of neurosis by dividing the patients into groups showing hysterical, phobic, or obsessional features. In contrast to previous findings no difference in response was found.

It is pointed out that an equally good result might be obtained with chlordiazepoxide in a daily dosage of 10 mg. instead of 20 mg., and that larger doses of amylobarbitone (100 mg.) would be more effective but at the price of increased drowsiness. The out-patients in this trial, however, were endeavouring to live normal lives and could not take these doses. *E. H. Johnson*

1278. **Procaine in the Treatment of the Neuroses of the Menopause.** (Лечение новокаином климактерических неврозов)
K. N. CUCUL'KOVSKAJA. *Советская Медицина* [*Sovetsk. Med.*] **25**, 79–85, April, 1961. 1 fig., 19 refs.

Procaine has been shown to possess analgesic, anticholesterolase, spasmolytic, antihistaminic, and antitoxic activity. After its administration the excitation and inhibition processes of the cortex are both augmented, the development of conditioned reflexes facilitated, and the activity of subcortical centres and visual and auditory analysers increased. The initial effect of procaine on higher nervous activity is one of disinhibition, an effect which becomes of particular value if excessive (pathological) inhibition is present.

In this study 140 female patients aged from under 35 to 65 years suffering from menopausal neurosis were treated with the drug. They were divided into three groups depending on the severity of symptoms (number of flushes per day). The manifestations of menopausal neurosis were associated with normal menstrual function in 33 cases, disturbed menstrual function in 32, amenorrhoea in 40, and the menopause proper in 20. In 11 patients they developed following hysterectomy, in one after x-ray castration, and in 3 after menopausal bleedings. A majority of the patients had already been

treated with hormones, irradiation of the pituitary gland, vitamins, physiotherapy, bromides, or hypnosis. Procaine was administered by slow intramuscular injection of 3, 5, or 10 ml. of a freshly prepared 2% solution in saline or in 5% glucose (*p*H 4·4), the injections being given on alternate days and the dose increased by 1 ml. at each session. Each course of treatment consisted of 12 injections and the interval between courses was 10 days. Patients with "a weak type of nervous system" tolerated the injections poorly and could be given no more than 3 to 5 ml. at a time. In 4 cases (2·9%) the treatment had to be discontinued because of intolerance.

Complete disappearance of symptoms was observed in 36·4% of the cases, considerable improvement in 33·6%, some improvement in 20%, and no change in 7·1%. The more severe the condition, the more courses of treatment were necessary; thus 4 courses were required in 9 cases, 3 in 40, 2 in 35, and one in 43. Following the treatment vaginal smears showed increased oestrogen saturation. A normal menstrual cycle was re-established in 27 patients. Frequent electrocardiograms and blood-pressure measurements showed the absence of toxicity of the drug when given as described.

In a further study 30 patients were treated with procaine in combination with "tropatsin" (synthesized in the U.S.S.R. in 1958) in a dosage of 0·01 g. twice daily for 7 to 10 days. The latter preparation reduces the reactivity of vegetative ganglia to chemical stimuli. The results in 22 of these 30 patients were good.

S. W. Waydenfeld

AFFECTIVE DISORDERS

1279. **A Controlled Trial of Imipramine ("Tofranil") in the Treatment of Severe Depressive States**
L. Rees, A. C. Brown, and S. Benaim. *Journal of Mental Science* [*J. ment. Sci.*] **107**, 552–559, May [received July], 1961. 15 refs.

At the Bethlem Royal and Maudsley Hospitals, London, the authors tried the effect of imipramine in 20 cases of severe depressive illness. They stress the importance of a really carefully controlled trial and themselves adopted a triple-blind procedure, using active and inert tablets. A preliminary period of observation of 10 to 14 days preceded the clinical trial. Each patient received both active and inert tablets for fixed periods, thus acting as his own control. The nature of the tablets was not known to patient, nurse, or physician, all of whom gave opinions as to progress, assessed after 3 and 6 weeks of treatment.

Cure or marked improvement was obtained with imipramine in 7 (35%) of the 20 patients, the corresponding figures for inert tablets being 2 (10%). With lesser degrees of benefit there was little difference between control and treated groups. There was greater improvement in anxiety and insomnia with imipramine than with inert tablets, but no difference between the two treatments as regards retardation, hypochondriasis, anorexia, and paranoid ideas. Seven patients receiving imipramine had dryness of the mouth or sweating, otherwise there were no important side-effects.

The authors conclude that, while imipramine improves some depressive illnesses, their results are not as good as those reported in the literature generally and suggest that this may be due to their more carefully controlled trial. They found that electric convulsion therapy produced a marked benefit in some cases in which imipramine had failed.

Gavin Thurston

1280. **A Controlled Trial of Phenelzine ("Nardil") in the Treatment of Severe Depressive Illness**
L. Rees and B. Davies. *Journal of Mental Science* [*J. ment. Sci.*] **107**, 560–566, May [received July], 1961. 20 refs.

The authors, at the Bethlem Royal and Maudsley Hospitals, London, made a controlled study of the effect of phenelzine ("nardil") in 21 cases of severe depression. A carefully planned triple-blind method was used and the clinical features were noted week by week. Patients acted as their own controls, receiving phenelzine and inert tablets for 3 weeks each, those given the drug for the first period having inert tablets for the second period and vice versa. The dosage of phenelzine was 2 tablets 3 times a day, giving a daily dose of 90 mg. One patient was withdrawn because of the development of jaundice during the first week of the trial, but this patient was subsequently found to have been taking inert tablets.

Complete symptomatic recovery or marked improvement was obtained with phenelzine in 50% of patients as compared with 15% with inert tablets. However, 13 of the patients had to have electric convulsion therapy to produce a complete recovery, and the authors conclude that shock treatment is more effective than phenelzine in severe depression. There were only minor side-effects, including oedema of the ankles and hypotensive symptoms (2 cases each).

It is concluded that phenelzine is an effective treatment in depressive illnesses, but it is possible that better results may be obtained in moderate or mild depression than in these severe cases.

Gavin Thurston

SCHIZOPHRENIA

1281. **Continued Studies on the Effect of Ceruloplasmin Administration in Schizophrenic Patients**
S. Mårtens, S. Vallbo, K. O. Kyhlberg, and C. O. Jonsson. *Journal of Neuropsychiatry* [*J. Neuropsychiat.*] **2**, 238–245, June, 1961. 1 fig., 12 refs.

The hypothesis that ceruloplasmin forms part of a protective system and that this system may be faulty in patients with schizophrenia was tested, results being discussed in this paper from Beckomberga Hospital, Bromma, Sweden. Preliminary studies had shown some promise, but revealed certain sources of error which are described; these were avoided in the present study, in which 28 patients with acute, subacute, or chronic schizophrenia were examined independently by two psychiatrists and their symptoms rated. The control group of patients were given a placebo in the form of a 5% albumin solution (coloured blue to look like ceruloplasmin) while in the treatment group each patient

received one intravenous injection of 1 g. of ceruloplasmin daily for 10 days. The environment was controlled, and the observers were unaware to which group a patient belonged.

Both observers found independently that there was a significantly greater improvement following the ceruloplasmin injections than after a similar number of placebo injections. The results of psychological tests showed a similar improvement in those given ceruloplasmin injections. These injections were accompanied by an increase in the serum copper level and in serum oxidative activity, and also by a decrease in total serum ascorbic acid content. It is noted that the improvement was most marked in acute and paranoid patients. The authors emphasize that the therapeutic effect of ceruloplasmin is not necessarily specific for schizophrenia and that this treatment is not claimed as a cure for the disease.

B. M. Davies

1282. **A Double-blind Trial to Investigate the Effects of Thorazine (Largactil, Chlorpromazine), Compazine (Stemetil, Prochlorperazine) and Stelazine (Trifluoperazine) in Paranoid Schizophrenia**

I. C. Wilson, J. McKay, and M. G. Sandifer Jr. *Journal of Mental Science* [*J. ment. Sci.*] **107**, 90–99, Jan. [received March], 1961. 1 fig., 26 refs.

It has been claimed that different members of the phenothiazine group of drugs have special therapeutic effects on certain symptoms—for example, that chlorpromazine controls aggression, but does not effect delusional thought disorder, while "stemetil" (prochlorperazine) influences delusions and psychomotor activity. Similarly "stelazine" (trifluoperazine) is said to alleviate delusional ideas and to activate withdrawn apathetic patients. The present authors have examined this differential therapeutic effect of three phenothiazine compounds. A group of 8 female paranoid schizophrenic patients were selected and in a similar environment were given chlorpromazine, prochlorperazine, trifluoperazine, and a placebo in a double-blind latin-square design trial. The Malamud–Sands rating scale was used and the ratings then subjected to statistical analysis. It was found that prochlorperazine and trifluoperazine were definitely superior to the placebo in controlling symptoms, while chlorpromazine, though better than the placebo, was not as effective as the other drugs. None of the drugs had an appreciably different effect on psychotic ideation.

B. M. Davies

1283. **Pineal Extract and Chronic Schizophrenic Behaviour**

H. M. McBryde, J. B. Knowles, and C. J. Lucas. *Archives of General Psychiatry* [*Arch. gen. Psychiat.*] **4**, 494–500, May, 1961. 9 refs.

This paper from the Medical Research Council Clinical Psychiatry Research Unit at Graylingwell Hospital, Chichester, reports the effects of intramuscular injections of protein-free alkaline extract of bovine pineal gland on the behaviour of a group of female patients with chronic schizophrenia. The method of preparation of the extract is described and follows closely that of Altschule (*New Engl. J. Med.*, 1957, **257**, 919; *Abstr. Wld Med.*, 1958, **23**, 377) who had observed that the blood glutathione level was low in psychotic patients and that it rose after injection of pineal extract, while the urinary ketosteroid output fell. He also described remissions in chronic schizophrenia associated with these biochemical changes.

Two groups each of 4 patients were matched for age, duration of illness, clinical assessment, and score on the Wittenborn Psychiatric Rating Scales. One group received pineal extract, the other saline, by intramuscular injection daily for 4 weeks. Behaviour was rated on the Wittenborn scales at weekly intervals for 8 weeks, beginning 2 weeks before treatment started; clinical and biochemical observations were also made.

There was no significant difference between the two groups in behaviour whether measured on the scale or assessed clinically. In neither group were there any marked changes in blood sugar and blood glutathione levels or in 24-hour urinary ketosteroid output.

The authors suggest that their failure to obtain the clinical and biochemical results reported by Altschule may have been due to failure to prepare an identical extract, since they noted an immediate sensitivity reaction (skin weal and tenderness) and pyrexia for 4 days after an injection—effects not described by Altschule. Possible causes of inactivation of the extract are considered.

Christopher Wardle

TREATMENT

1284. **Psychodynamic and Psychotherapeutic Problems in Connection with Imipramine (Tofranil) Intake**

H. Azima. *Journal of Mental Science* [*J. ment. Sci.*] **107**, 74–82, Jan. [received March], 1961. 7 refs.

In this investigation reported from McGill University and Allen Memorial Institute, Montreal, an attempt was made to delineate the effects of imipramine on psychodynamic structure and to apply these to the psychotherapy of depressive illnesses. It was found that imipramine altered the depressed mood and that there was a decrease in guilt feelings, with a change from an undue preoccupation with internal object relationships to external object relationships. In addition, aggressive tendencies previously directed inwards were turned outwards, with a secondary effect on libido.

The action of imipramine is discussed from the viewpoint of psychoanalytic theory and practical recommendations made. Imipramine was found to be useful in the initial stage of psychoanalysis of patients with severe depression and in depressive episodes occurring during analysis.

B. M. Davies

1285. **The Placebo Effect in Psychiatric Drug Research**

A. W. Loranger, C. T. Prout, and M. A. White. *Journal of the American Medical Association* [*J. Amer. med. Ass.*] **176**, 920–925, June 17, 1961. 6 refs.

The majority of studies undertaken to evaluate tranquillizer and antidepressant drugs are uncontrolled and Heilizer (*J. chron. Dis.*, 1960, **11**, 102) concluded that some 90% of such studies fall short of minimum stan-

dards of scientific acceptability. In an attempt to investigate the practical significance of such an approach the authors devised a trial in which, unknown to the psychiatrists, nurses, and patients, only placebos were used. The investigation was presented as an evaluation of two new drugs, a tranquillizer and an "energizer", and all the usual methods of a genuine trial were employed. The test was carried out on 120 patients selected from admissions over a one-year period to the Westchester (Psychiatric) Division of the New York Hospital; convalescent and very agitated or depressed patients were not included. Those with recent or predominant symptoms of anxiety, hostility, or hyperactivity were assigned to the tranquillizer study and those with depressive features to the energizer study. As far as possible patients within each study were matched and randomly allocated to a "control" or "drug" group. The latter received a 6-week course of the respective "drug", this being preceded and followed by a 2-week "no-drug" period as in a real trial. All the patients were receiving concurrent psychotherapy. Following the protocol used in many uncontrolled studies, the patients, psychiatrists, and nurses completed a weekly 6-point rating of response which ranged from "worse" to "helped a great deal".

Depending on the informant, these ratings showed that 53% to 80% of the (60) patients given the "drug" were said to have been helped for an average of 2·6 to 4·9 of the 6 weeks of its administration. Such results are similar to those reported in comparable uncontrolled drug studies. In order further to investigate the controlled method of evaluating treatment, head nurses were asked to complete a weekly 9-item behavioural rating scale for both "treated" and control patients. When the scores were adjusted for pre-treatment levels, analysis of co-variance showed that patients receiving the tranquillizer achieved a significant but temporary improvement, but no significant differences at all emerged in those given the energizer.

While it is emphasized that appropriate experimental design is a necessary but not sufficient condition for a drug trial to yield worthwhile results, the present findings clearly illustrate the dubious value of studies which neglect double-blind and other control procedures.

Alan A. Black

1286. **Negative Results with Chlorpromazine and Benactyzine in a Group of Chronic Psychotics, with Critical Evaluation of Similar Studies**

T. A. Loftus, D. L. Clark, F. R. Crouse, T. E. Dillon, D. J. Jones III, and H. E. Lefever Jr. *Psychiatric Quarterly* [*Psychiat. Quart.*] **35**, 121–133, 1961. 1 fig., 28 refs.

Since personal observation failed to confirm reports of marked improvement following administration of tranquillizers, it was felt that such reports reflect unsuspected errors in evaluation. Among these the present authors would include inadequate data on quantification of change, on milieu and non-specific effects, and on chances of spontaneous recovery, and in the trial here reported from Jefferson Medical College, Philadelphia, they tried to eliminate such sources of error. Ruling out brain-damaged and retarded patients, 120 chronic, "backward" psychotics were randomly divided into two equal groups. During a 5-week baseline study in which all drugs were stopped 18 of these patients were removed from the trial, mainly because muteness precluded thorough investigation. Five others were excluded during the period of drug administration because of side-effects. The remaining 97 patients (93 schizophrenics) received either chlorpromazine or benactyzine for 11 weeks, using a double-blind technique. Initial doses of 150 mg. of chlorpromazine or 15 mg. of benactyzine daily were doubled after 3 weeks and trebled after 7 weeks. Throughout the trial there was no other change in the established custodial care of these patients. Detailed psychiatric assessments were made during the 5th week of the baseline study and during the 11th week of drug administration; these data were transcribed for each patient to yield component reaction scores and an index of psychopathology on the Lorr Multidimensional Scale for Rating Psychiatric Patients. Comparison of the two groups of patients showed that they were similar as to age, chronicity, and pre-drug severity of illness. After 11 weeks' treatment no clinically or statistically significant change occurred in response to either drug.

The authors conclude that the degrees of remission reported in comparable studies may be due to factors other than specific drug action, diagnostic category, component reactions, or problems of management.

Alan A. Black

1287. **A Comparative Study of Selected Tranquilizers in the Treatment of Psychiatric Patients**

E. C. Toms. *Journal of Nervous and Mental Disease* [*J. nerv. ment. Dis.*] **132**, 425–431, May [received July], 1961. 4 figs., 16 refs.

This study was a controlled evaluation of the relative therapeutic effectiveness of meprobamate and prochlorperazine in the treatment of mildy disturbed mental patients, and chlorpromazine and perphenazine in the treatment of severely disturbed patients. Patients were male veterans, new admissions to a neuropsychiatric hospital who had not received tranquilizing medication for at least 3 months prior to admission. Patients were evaluated before and after treatment by means of a personality inventory and a behaviour rating scale.

For comparable groups of mildly disturbed mental patients, meprobamate and prochlorperazine differ in therapeutic effectiveness. Meprobamate seems to have a greater tranquilizing effect on overt behavioral manifestations, which resulted in improved social relations on the part of the patients, while patients on prochlorperazine showed considerable improvement in mental symptoms. Compared with perphenazine, chlorpromazine appears to produce more variable effects on patients, which suggests that patients should be carefully chosen for treatment with chlorpromazine. Chlorpromazine seems to be much more effective than perphenazine in reducing depression and paranoid mentation. As compared with chlorpromazine, patients on perphenazine showed more improvement in ward behavior, but less improvement in mental condition.—[Author's summary.]

Paediatrics

1288. **Experimental Studies on the Prevention of Rh Haemolytic Disease**
R. FINN, C. A. CLARKE, W. T. A. DONOHOE, R. B. MCCONNELL, P. M. SHEPPARD, D. LEHANE, and W. KULKE. *British Medical Journal* [*Brit. med. J.*] **1**, 1486–1490, May 27, 1961. 2 figs., 18 refs.

Haemolytic disease of the newborn usually arises when the mother is Rh negative and the foetus Rh positive, probably as a result of a small quantity of foetal blood "leaking" across the placenta into the maternal circulation and stimulating the production of antibodies. There is evidence that ABO incompatability between mother and foetus affords some protection against Rh sensitization. The authors, writing from the University of Liverpool, describe work to confirm these suggestions and preliminary studies to test a possible means of preventing haemolytic disease.

Investigation of a series of 63 families with Rh-negative mothers and Rh-positive fathers in which 4 or more children had been born, yet no Rh sensitization had occurred, revealed that in 42·9% of cases the mother and father were ABO incompatible compared with 33·6% in the general population and 22·0% in a previous investigation of families with haemolytic disease. A sensitive test for foetal erythrocytes in maternal blood depends on the differential elution of foetal and maternal haemoglobin by means of citric–phosphate buffer in a normal blood smear, the adult cells appearing as ghosts while the foetal cells stand out as dark refractile bodies. A modification of this technique was used to study post-partum blood smears from 256 women. All were unselected for parity and ABO group and all but the first 50 were known to be Rh negative. A "foetal cell score" was allotted to each sample depending on the numbers of foetal erythrocytes counted in two 3-minute counts; earlier studies with mixtures of adult and foetal blood showed that a "foetal score" of 5 indicated a bleed of approximately 1 ml. of foetal blood into the maternal circulation. A foetal score of 2 or more was found in 30 of the 256 samples, but in only 4 did the score suggest a bleed of 5 ml. or more. The serum from 85 of the Rh-negative women in this series who were delivered of an Rh-positive infant was tested for Rh antibodies 2 or 3 months after parturition. One of the 75 who apparently did not receive foetal blood developed antibodies (these were anti-C), none of the women with evidence of "small" bleeds developed antibodies, but 2 out of the 3 with a foetal score of 20 or more ("large" bleed) developed antibodies. There is a statistically significant association between large bleeds and antibody formation.

Six male volunteer blood donors of Group A cde/cde were given an intravenous injection of 5 ml. of Group A CDe/cde blood labelled with radioactive chromium (^{51}Cr). Half an hour later 3 were given 10 ml. of anti-D serum having a titre with the donor cells of 1:64 in saline and albumin. Subsequent studies showed normal survival of Rh-positive cells in men not given anti-D in contrast to the disappearance of at least 50% of the donor cells after 2 days in the 3 subjects given anti-D; furthermore, the surviving Rh-positive cells in these 3 were coated with anti-D.

Certain problems are yet to be solved, but these experiments suggest that an efficient method may be found for preventing Rh sensitization and subsequent haemolytic disease of the newborn. *F. P. Hudson*

1289. **Purulent Meningitis of Newborn Infants: Eleven-year Experience in the Antibiotic Era**
R. V. GROOVER, J. M. SUTHERLAND, and B. H. LANDING. *New England Journal of Medicine* [*New Engl. J. Med.*] **264**, 1115–1121, June 1, 1961. 1 fig., 27 refs.

Experience of purulent meningitis in newborn infants between 1948 and 1959 at the General and the Children's Hospitals, Cincinnati, is reviewed, the authors [forlornly] stating that "the prognosis is little better to-day than thirty years ago". A group of 39 infants (20 male and 19 female) under 28 days old at the time of onset of proven purulent meningitis were studied. Gram-negative enteric organisms accounted for 16 cases, Gram-positive cocci for 9, and other organisms for 4; in the remaining 10 cases no organism was identified. Of the 39 infants, 16 were premature by birth weight and 23 were born at full term. At the onset of the illness 25 infants were 10 days old or under and 12 of the 16 premature infants were less than 6 days old. Obstetric complications, which increase the morbidity and mortality rates in neonatal meningitis, were present in over half the cases, and included premature rupture of the membranes, birth trauma, and antepartum haemorrhage.

The difficulty of diagnosis is illustrated by the fact that this was delayed or missed in 14 of the premature infants and in 10 of those born at term. There were 26 deaths, a mortality of 66·6%; of the premature infants, 13 (81%) died during the acute illness compared with 13 (57%) of the mature infants. Neither the causative organism nor the type of antibiotic therapy bore any significant relation to the outcome. The prognosis was best in mature infants with late onset of symptoms. The need for early diagnosis and treatment is emphasized.
David Morris

1290. **Meconium Peritonitis: Prognostic Significance**
B. SMITH and H. W. CLATWORTHY JR. *Pediatrics* [*Pediatrics*] **27**, 967–970, June, 1961. 2 figs., 15 refs.

An analysis is presented of the results achieved in 31 newborn infants with meconium peritonitis seen at the Children's Hospital, Columbus, Ohio, during the 12-year period 1947–59. Of these, 10 survived and have remained well. It is pointed out that the diagnosis is not difficult, the symptoms being those of neonatal

intestinal obstruction with distension, bilious vomiting, and abnormalities in meconium evacuation. Maternal hydramnios is often a concomitant finding. The radiological appearances of the abdomen may be diagnostic, since in the majority of cases the intraperitoneal meconium calcifies and such calcifications, together with other evidence of obstruction, may be visible.

The cause of the prenatal perforation is usually obvious at operation and may be meconium ileus, intestinal atresia, or extrinsic obstruction such as strangulation in an internal hernia. In most instances the perforation is sealed off by plastic exudate, but occasionally the perforation may remain open with a consequent massive pneumoperitoneum. It is only rarely that the cause cannot be found. In the present series the cause was either meconium ileus or intestinal atresia. Of the 31 patients, 6 were not operated on and all died; of 10 in whom the cause was meconium ileus with cystic fibrosis, only one survived; of 15 in whom the meconium peritonitis was unassociated with ileus, 9 survived.

The surgical treatment recommended is resection of the matted intestine, including the bulbous, poorly functioning portion proximal to the site of obstruction. Postoperative intestinal decompression by gastrostomy or catheter enterostomy through the stump of the appendix is advised. It is the authors' view that provided 50% or less of the intestine is resected the child will thrive, but resection of amounts greater than this are associated with insurmountable nutritional problems.

Andrew M. Desmond

1291. **A Longitudinal Study of the Growth and Development of Prematurely and Maturely Born Children. Part VII: Mental Development 2–5 Years**

C. M. DRILLIEN. *Archives of Disease in Childhood* [*Arch. Dis. Childh.*] **36**, 233–240, June, 1961. 4 figs., 11 refs.

In this paper from the University of Edinburgh the author continues a study of the growth and development of prematurely born children. [For the earlier papers see *Abstr. Wld Med.*, 1959, **25**, 204, and **26**, 125; 1960, **27**, 71, and **28**, 69; and 1961, **30**, 70.] Of the original 600 children (premature, with full-term controls), 92% of the survivors remained in the survey at 3 years and 90% at 4 years. They were examined at 6-monthly intervals up to the age of 2 years and annually thereafter. Mental tests were those of Gesell and of Terman and Merrill. About half the group have now entered school.

As at 2 years, mean scores on intelligence testing fell steadily at 3, 4, and 5 years with increasing birth weight. Twins had consistently lower scores than singletons of comparable birth weight. At 4 and 5 years there was a striking excess of children with a birth weight under 4½ lb. (2 kg.) who were unsuitable for education at school or were educationally subnormal.

The author states that the expected response to preschool developmental tests is affected by birth weight, environment, and opportunity. She found [as others have done] that it is much easier to predict mental dullness in infancy than mental superiority. Of 16 children considered to be unsuitable for education at an ordinary school (I.Q. less than 70), 12 were assessed at this level at 6 months and at every subsequent examination; no child scored higher than "very dull" at any test at any age. Of 16 considered "border-line" defective in school (I.Q. 70 to 79), 12 were rated at this level or lower from the age of 6 months.

R. S. Illingworth

1292. **"Uncomplicated" Hyperbilirubinemia of Prematurity. The Lack of Association with Neurologic Deficit at 3 Years of Age**

J. G. SHILLER and W. A. SILVERMAN. *American Journal of Diseases of Children* [*Amer. J. Dis. Child.*] **101**, 587–592, May, 1961. 9 figs., 17 refs.

In the premature nursery of the Babies Hospital, New York, 188 infants were examined clinically and the serum bilirubin level was determined daily during the first week of life. Of these, 110 were followed up for 3 years; of the remaining 78, 46 died (one from kernicterus) and 32 survived but were lost to follow-up.

The neurological and mental status of the children seen at 3 years of age was assessed, and a comparison made between those in whom in the neonatal period the serum bilirubin level was above 18 mg. per 100 ml. and those in whom the bilirubin level did not exceed this value. There appeared to be no difference between the "high" and "normal" bilirubin groups in respect of the incidence of hypotonia, spasticity, speech defect, mental retardation, or behaviour disorders. In none of the patients were the classic features of kernicterus found. The authors suggest that premature infants may be able to tolerate high serum concentrations of bilirubin when this state is not complicated by erythroblastosis, administration of excessive doses of vitamin K, or administration of "sulfisoxazole" (sulphafurazole).

R. M. Todd

CLINICAL PAEDIATRICS

1293. **Spiramycin in the Treatment of Infections in Children: *in vivo* and *in vitro* Studies**

J. JELJASZEWICZ and M. GONCERZEWICZ. *International Record of Medicine* [*Int. Rec. Med.*] **174**, 80–87, Feb. [received April], 1961. 10 refs.

Spiramycin was given to 102 children, aged 12 days to 24 months, suffering from purulent pleuritis (9), pneumonia (18), furunculosis (17), septicemia (10), otitis media (19), pharyngitis (15), or toxic diarrhea complicated by purulent otitis media and arthritis (14). The drug was given orally in a dosage of 40 to 60 mg. per kg. body weight daily in four divided doses. The best results were obtained in pharyngitis and furunculosis, as all the children recovered very quickly. Good results were also obtained in all other infections except that of complicated toxic diarrhea. In this group, only 4 of 14 children responded to spiramycin treatment. Of the total of 102 children, very good results were obtained in 65 cases, satisfactory in 18 children, and no improvement in 19 patients, all of whom had diarrhea. Staphylococci were isolated from the pathological material, as well as from the throats of carriers, before, during, and after treatment. A total of 297 strains were tested for sensitivity to penicillin, streptomycin, chlortetracycline, oxy-

tetracycline, chloramphenicol, tetracycline, oleandomycin, oleandomycin–tetracycline, spiramycin, and erythromycin. It was found that these strains were most susceptible to the action of antibiotics from the erythromycin group (spiramycin, oleandomycin, and erythromycin), oleandomycin–tetracycline, and chloramphenicol. The number of resistant strains harbored by carriers was greater at the time of leaving the clinic. No serious symptoms of intolerance of spiramycin were observed. A total of 193 strains of staphylococci were studied for ability to form various toxins and for possession of several biochemical properties (α, β, and δ-hemolysins, free and bound coagulases, staphylokinase, leukocidin, urease, lipase, gelatinase, phosphatase, *aureus* pigment, anaerobic fermentation of mannitol and glucose, ability to grow in normal human serum). Eventual correlation between the source of strains and free coagulase titer in staphylococcal culture *in vitro* was investigated.—[From the authors' summary.]

1294. **Iron-deficiency Anaemia in Children and Its Treatment with Iron Poly*iso*maltosate.** (Die Eisenmangelanämie des Kindes und ihre Behandlung mit Eisen-Polyisomaltosat)
T. Mereu and O. Tönz. *Deutsche medizinische Wochenschrift* [*Dtsch. med. Wschr.*] **86**, 1259–1266, June 30, 1961. 5 figs., bibliography.

Iron poly*iso*maltosate (" ferrosanol ") is a preparation of iron suitable for intramuscular injection which has been shown to be free of carcinogenic action when given to animals in large doses. At the University Paediatric Clinic, Berne, the authors have tried it in the treatment of 29 children ranging in age from 4 months to 14 years with initial haemoglobin concentrations of less than 10 g. per 100 ml. and the haematological picture of iron-deficiency anaemia. Injections were given daily or on alternate days, the total dose of iron varying from 100 to 600 mg. according to body weight and initial haemoglobin level; (2 ml. of the preparation contained 100 mg. of elemental iron).

In all cases the result was satisfactory as judged by the reticulocyte response and rise in haemoglobin level, haematocrit value, and mean corpuscular haemoglobin concentration, while the blood picture became more normal. Pain was sometimes felt at the site of injection for up to 24 hours and some of the infants showed a transient pyrexia. *P. C. Reynell*

1295. **Empyema in Childhood**
E. Hoffman. *Thorax* [*Thorax*] **16**, 128–137, June, 1961. 9 figs., 7 refs.

Between 1941 and 1958 125 patients aged under 13 were admitted to Shotley Bridge Hospital, Newcastle upon Tyne, with pleural empyema. The annual admission rate fell during 1944–50, probably owing to the introduction of antibiotics, and then remained steady, although the admission rate for children under 2 years has recently risen. In 76 of the cases empyema followed pneumonia. Pneumococci were the commonest organisms cultured from pleural pus, with staphylococci next; many cultures were sterile. Staphylococcal empyema was most common in children under 2 years. The author states that empyema occurring in the first 12 months of life is likely to be of staphylococcal origin. It is often accompanied by pneumothorax, sometimes under tension, or pneumatocele or lung cysts due to lung distension. These cysts may rupture, but usually disappear without permanent damage; in 2 cases in the present series operation was necessary. Complications, which occurred in 26 of the 125 cases, included pyaemia, osteomyelitis of the ribs, and bronchiectasis. In 13 cases there was chronic empyema which had frequently not been recognized.

Antibiotics are of primary importance in treatment, which must be based on the known or suspected causative organism. Early evacuation of pus by aspiration or drainage with full re-expansion of the lungs is essential. Rib resection is seldom necessary. Major surgery, usually pleurectomy, was needed in a few cases in the present series. Bronchography, which was carried out at a late stage on 56 patients, revealed a normal bronchial tree in 41; in 7 patients, most of whom had chronic empyema, there was severe bronchiectasis. There were 5 deaths; 4 were due to empyema and one followed an operation for bronchiectasis. *M. Meredith Brown*

1296. **The Role of Thyroid Dysgenesis in Delayed Hypothyroidism in Children.** (Le rôle de la dysgénésie thyroïdienne dans les hypothyroïdies tardives de l'enfant)
N. Neimann, M. Pierson, M. Wayoff, J. Martin, and X. Berthier. *Archives françaises de pédiatrie* [*Arch. franç. Pédiat.*] **18**, 213–222, Feb. [received July], 1961. 5 figs., 7 refs.

In this report from the Faculty of Medicine of Nancy the authors describe 7 children who all developed signs and symptoms of hypothyroidism, 6 of them in the first 3 years of life and the 7th at the age of 12 years. In all 7 cases the gland was demonstrated to have failed to descend to its normal position in the neck, being situated at the base of the tongue in 6 cases and described as lying above the hyoid bone in the remaining case. The position of the gland was demonstrated by the use of radioactive iodine in 6 cases, but in the 7th, though hypothyroidism had developed earlier, the gland enlarged at puberty and when the patient was aged 16 led to obstruction of the pharynx. At operation it was found to be lying at the base of the tongue and was transplanted to the submaxillary region.

The authors conclude that the cause of hypothyroidism in this type of case is failure of descent of the gland and the resulting inadequate development of gland tissue. They extend their argument, however, to include cases of congenital myxoedema. *H. G. Farquhar*

1297. **Normal Head Growth and the Prediction of Head Size in Infantile Hydrocephalus**
E. M. O'Neill. *Archives of Disease in Childhood* [*Arch. Dis. Childh.*] **36**, 241–252, June, 1961. 13 figs., 10 refs.

A study of maximum head circumference measurements was made on normal full-term and premature babies. The survey was a longitudinal one and all

measurements were taken personally; 676 full-term and 225 premature babies were involved and a total of 4,639 measurements was taken from these 901 infants. In the majority of cases head circumference values were obtained at birth and then at weekly and later fortnightly intervals up to 18 and 26 weeks of age from full-term and premature babies respectively.

From the material collected in the head circumference survey the following were obtained: (1) A graph to show the normal range of head circumference in relation to age in full-term infants from birth to 18 weeks. (2) A head circumference/age chart to show the normal range of head size in premature babies from birth to 26 weeks of age. (3) A chart to show the normal range of head circumference at one week of age relative to birth weight. This covered a weight range of 3 to 9 lb. [1·36 to 4 kg.] and therefore included premature as well as full-term infants. (4) Control lines. These were described with special emphasis on their significance and their use in association with a ratio chart. The "lines" presented were drawn at weekly intervals from 1 to 16 weeks for both full-term and premature babies. Each control line represents a maximum normal rate of head circumference increase.

A method has been described for predicting the head size of any individual at one year of age in terms of defined groups. This technique resulted from an empirical modification of the use of control lines and depends on a knowledge of the maximum normal head circumference at birth relative to the birth weight. The predictions are made between birth and 16 weeks of age. The following results emerged from the application of this method to cases in the present series: (1) An accurate forecast of the Group indicating head size was made in 90% of 99 cases. (2) Warning of the impending change of Group was given in just less than half of the Group 2 cases. In three-quarters of the Group 3 patients an accurate prediction of the final head size was made 4 or more weeks in advance of the change and in the remainder at least one week of warning was given in each case.

Three examples, forecast correctly to reach Groups 1, 2, and 3, were given. All 3 had a very rapidly progressive hydrocephalus, but it was possible during the progressive phase, to distinguish between early, moderately early, and late arrest by the technique described in this report.—[Author's summary.]

1298. **Cerebral Palsied Twins**

E. M. Russell. *Archives of Disease in Childhood* [*Arch. Dis. Childh.*] **36**, 328–336, June, 1961. 2 figs., 26 refs.

Of 488 cerebral palsied patients seen at the Edinburgh Clinic of the Scottish Council for the Care of Spastics between 1949 and 1956, 45 were twins and one a triplet. One twin whose data were incomplete was omitted, as was the triplet, and the remaining 44 patients were matched with controls. The highest incidence of twins was found in the diplegic group of patients, where over 40% were premature at birth. The average birth weight of 38 cerebral palsied twins (the 6 twins whose partner was a macerated foetus being excluded) was 4 lb. 3 oz. (1·899 kg.), of their 20 surviving healthy twins 4 lb. 13 oz. (2·183 kg.), of the 14 stillborn and dead twins 3 lb. 8 oz. (1·586 kg.), and of the controls 5 lb. 5 oz. (2·409 kg.). Prematurity therefore seems to be the significant factor, but the fact that pre-existing foetal abnormality may cause premature birth may account for the incidence of 68% of the cerebral palsied twins who had abnormal neonatal signs compared with 18% of their healthy twins and 13% of the controls. Less than half had surviving healthy twins, 23% dying neonatally compared with 6·8% of controls, and 6 being macerated foetuses, of which there were none in the control group.

No significant differences were found in maternal ages, reproductive histories, abnormalities of parturition, or pregnancy except for a higher incidence of uterine haemorrhage—10 as compared with one in the control group.

Of the cerebral palsied twins 63% were first-born, but most of the stillborn and dead in the series were second-born. The ratio of like-sexed to unlike-sexed was greater than in the controls, and a higher proportion of probable uniovular than binovular twins were affected.

Janet Q. Ballantine

1299. **Aetiology of Erythema Nodosum in Children**

A Study by a Group of Paediatricians. *Lancet* [*Lancet*] **2**, 14–16, July 1, 1961. 5 refs.

A study of the aetiology of erythema nodosum was made in 82 cases of the disease collected by a group of paediatricians in 2 years. Children whose lesions had faded before examination were not included. The investigation comprised a Mantoux test, chest radiography, examination of a throat swab, and estimation of the anti-streptolysin-O titre at the first visit and again after 8 days. Other investigations were carried out when indicated.

The only two aetiological factors discovered were tuberculous and streptococcal infections. On Mantoux testing 41 of the 82 children were found to be tuberculin positive—9 (82%) of the 11 children under 5 years of age, 15 (58%) of the 26 between 5 and 10, and 17 (38%) of the 45 over 10. Of the children under 5 years old, 8 (73%) had active tuberculous lesions, compared with 10 (38%) in the 5 to 10 age group and 5 (11%) among those over 10. Of the 41 children who were tuberculin positive, 15 had a history of recent streptococcal infection. An antistreptolysin-O titre above 200 units was found in 46 children (56%), but only 11 children (13%) had a positive streptococcal throat swab. Four-fifths of the tuberculin-negative children had proved streptococcal infections. Only one child under 5 was considered to have erythema nodosum of streptococcal origin. Of the 15 children with a possible double aetiology, 7 had active tuberculous lesions and an antistreptolysin-O titre of less than 300 units; in the remaining 8 either the titre was over 300 units or β-haemolytic streptococci were isolated from the throat. In 8 children no satisfactory cause was found. Final assessment shows that "in 50% the evidence favours a streptococcal aetiology, in 41% it favours a tuberculous aetiology, and in 9% no aetiological agent was discovered". *J. G. Jamieson*

Medical Genetics

1300. **Detection of the Heterozygous Carrier of the Wilson's Disease Gene**

I. Sternlieb, A. G. Morell, C. D. Bauer, B. Combes, S. de Bobes-Sternberg, and I. H. Scheinberg. *Journal of Clinical Investigation* [*J. clin. Invest.*] **40**, 707–715, April, 1961. 4 figs., 41 refs.

A method for the detection of heterozygotes for the gene which in homozygotes results in Wilson's disease is described in this paper from the Albert Einstein College of Medicine, New York. It is based on a quantitative measure of the incorporation of radioactive copper (^{64}Cu) into ceruloplasmin, 2·0 mg. of ^{64}Cu as cupric acetate, with an activity of 0·5 to 2·0 mc., being administered following a fast of 8 hours or more and the ratio of the concentration of ^{64}Cu in the serum at 48 hours to that at 1 or 2 hours taken as a measure of the amount of ^{64}Cu incorporated into the copper protein.

The geometric mean of this ratio was shown to be 1·372 in 19 control subjects, 0·510 in 19 parents of patients with Wilson's disease, and 0·171 in 7 patients with the disease. Since both parents of a patient with Wilson's disease must be heterozygous for the gene the findings indicate that the gene in single dose has an appreciable effect on the incorporation of copper. Although there was admittedly some overlapping between the distribution of values for the control subjects and that for the parents, nevertheless it is concluded that the majority of subjects heterozygous for the abnormal gene can be detected by this procedure. *H. Harris*

1301. **Further Observations on an Inherited Anomaly Characterized by Persistence of Fetal Hemoglobin**

T. B. Bradley Jr., J. N. Brawner III, and C. L. Conley. *Bulletin of the Johns Hopkins Hospital* [*Bull. Johns Hopk. Hosp.*] **108**, 242–257, April, 1961. 3 figs., 20 refs.

This paper from Johns Hopkins University School of Medicine, Baltimore, adds yet another contribution to our knowledge of the peculiar condition in which the production of foetal haemoglobin persists into adult life without being associated with any obvious haemoglobinopathy. When this condition is inherited by a sickle-cell heterozygote only haemoglobins S and F are found and the electrophoretic pattern is indistinguishable from that seen in sickle-cell anaemia. Yet such heterozygotes are not anaemic and they suffer from no sickle-cell crises. The authors put forward an explanation for this apparent paradox. By ingenious differential haemolysis, carried out after deliberate mechanical damage to the erythrocytes, they succeeded in showing that in sickle-cell anaemia the haemoglobin F is not evenly distributed and that there are some erythrocytes with a high haemoglobin-F content and others which contain almost only sickle-cell haemoglobin. These latter cells would easily sickle even when the oxygenation was still within physiological limits. On the other hand in the heterozygote for the sickle-cell trait and the persistence of foetal haemoglobin haemoglobin F is evenly distributed in all cells, thus reducing their liability to sickle.

H. Lehmann

1302. **Genetics of Familial Mediterranean Fever (FMF): a Disorder with Recessive Inheritance in Non-Ashkenazi Jews and Armenians**

E. Sohar, M. Prass, J. Heller, and H. Heller. *Archives of Internal Medicine* [*Arch. intern. Med.*] **107**, 529–538, April, 1961. 6 figs., bibliography.

Familial Mediterranean fever is a disease characterized by recurrent brief attacks of fever, with pain in the abdomen, chest, joints, or skin; the erythrocyte sedimentation rate is raised and proteinuria is common (Heller *et al.*, *Arch. intern. Med.*, 1958, **102**, 50). For this study the authors have collected 262 cases of the disease, including 141 seen by them personally at the Tel-Hashomer Hospital, Tel-Aviv, together with the data for a further 121 cases seen at other public hospitals in Israel. Sephardi and Iraqi Jews from "the wider Mediterranean area" including North Africa, of whom there are some 680,000 in Israel, accounted for 250 of the 262 cases. Only 6 cases occurred in Ashkenazi Jews with a population in Israel of 960,000, and 6 in Arabs. Full details for 30 of the cases were not available.

The 232 cases in which a family history was obtained occurred in 113 families (kinships), affecting one generation in 103 cases, two generations in 9, and three generations in one. There were 123 affected sibships containing 664 sibs, of whom 201 (30·2%) were affected and 463 unaffected. Using Weinberg's "sib method" it was shown that affected sibs themselves had 248 affected and 738 unaffected sibs, giving a ratio of 1:2·97, which is very close to the ratio of 1:3 expected for recessive inheritance. In each size of sibship the number affected did not differ significantly from the number expected on the same hypothesis. Nine affected parents had 43 children, of whom 21 were affected. First-cousin marriages accounted for 25 of the 136 marriages producing affected children, this frequency being nearly twice that estimated for consanguineous marriages in the general population; a similar excess was found when the material was analysed in three separate ethnic groups. The 232 cases analysed occurred in 135 male (58·2%) and 97 female (41·8%) patients, which it is noted is practically identical with the sex distribution in 180 cases of the disease collected from the literature, namely, 57% males and 43% females. The conclusion drawn is that familial Mediterranean fever is due to an autosomal recessive gene, with a frequency of at least 0·019 among non-Ashkenazi Jews.

G. C. R. Morris

1303. **XX/XO Mosaics in Turner's Syndrome**

J. de Grouchy, M. Lamy, J. Frezal, and J. Ribier. *Lancet* [*Lancet*] **1**, 1369–1371, June 24, 1961. 2 figs., 7 refs.

Public Health and Industrial Medicine

1304. **Effectiveness of Salk Vaccine in Reducing Non-paralytic Poliomyelitis in a Large Urban Epidemic**
W. M. MARINE, T. D. Y. CHIN, C. R. GRAVILLE, and M. E. SOERGEL. *New England Journal of Medicine* [*New Engl. J. Med.*] **264**, 903–907, May 4, 1961. 1 fig., 13 refs.

An outbreak of poliomyelitis Type 1 occurring in Kansas City, Missouri, in 1959 gave the opportunity to investigate the efficacy of Salk vaccination. There were 210 cases (an incidence of 42·0 per 100,000 population) 118 being paralytic and 92 non-paralytic, during the period June to October, the peak incidence being on July 15th. In 60% of cases the patient was under 5 years of age. A 60-day follow-up was possible in 207 cases. The diagnostic criteria for paralytic disease were muscle weakness for 60 days, and for non-paralytic disease a typical clinical history without muscle weakness, but with 10 or more leucocytes in the cerebrospinal fluid. In the assessment of vaccination status all injections given within 2 weeks of the date of onset of the illness were excluded.

A socio-economic survey of vaccination status carried out in June, 1959, showed the lowest levels to be among the poorer whites and negroes. The incidence of poliomyelitis in this population was found to be 124 per 100,000 for negroes and 17 per 100,000 for whites. Poliovirus Type 1 was the aetiological agent in 98·5% of paralytic and 87·5% of non-paralytic cases, while 12·5% of non-paralytic forms were due to other enteroviruses.

In 12% of the paralytic and 21% of the non-paralytic cases the patient had received three or more injections of Salk vaccine. The conclusion is therefore drawn that "among the triply vaccinated population Salk vaccine reduced nonparalytic disease 73·5% and paralytic disease 76·8%". *Kurt Schwarz*

1305. **An Outbreak of Human Infection Due to *Salmonella typhimurium* Phage-type 20a Associated with Infection in Calves**
E. S. ANDERSON, N. S. GALBRAITH, and C. E. D. TAYLOR. *Lancet* [*Lancet*] **1**, 854–858, April 22, 1961. 2 figs., 14 refs.

Between July and October, 1958, there occurred 55 "incidents" (a term used in this paper to mean either a sporadic case or an outbreak, that is, 2 or more related cases) of infection due to *Salmonella typhimurium* phage-type 20a and these were investigated at the Central Public Health Laboratory, Colindale, London. Kosher meat was at first suspected as a possible source, since in 17 incidents the patients were orthodox Jews. The incubation period, in the 2 incidents (21 cases) in which it could be ascertained, varied between 24 and 84 hours. Of the total of 90 patients involved, 42 were male and 42 female, of whom one died (in 6 cases the sex was not recorded), while of 56 patients whose ages were known, 40 were under age 20, and 22 under 5, the incidence thus being highest in the young. In 4 cases, because of the severe abdominal pains, appendicectomy was performed and only later was the cause of the enteritis identified as being due to *S. typhimurium*. In some cases the onset was febrile and was followed after 24 hours by diarrhoea.

Early in the outbreak some sick calves, all purchased from the same collecting centre near Oxford, were shown to be harbouring *S. typhimurium* phage-type 20a. This finding led to the investigation of veal and calf products as the source of the infection. In 33 incidents involving calf meat, 18 were associated with its consumption, 4 occurred in those handling it, and 11 were indirectly connected with it. Though no samples of the suspected meat could be obtained, veal seemed to be the obvious source of infection in three-fifths of the incidents. At one London abattoir receiving animals from the Oxford collecting centre mentioned above 12·7% of rectal swabs of apparently healthy calves showed the presence of *S. typhimurium* phage-type 20a. The infection rate was highest in those animals kept together longest (up to 5 days) at the collecting centre, where cross-infection was most likely to occur. It is pointed out that this study shows the value of phage-typing in the investigation of *S. typhimurium* infections, as it clearly linked up scattered outbreaks occurring over 4 months and as far apart as Manchester, London, and Brighton. Thus the clue provided by the routine phage-typing of strains from sick calves on a farm as type 20a led from the farm to the collecting centre and thence to the abattoirs where the same type was isolated from slaughtered calves. Though the principal vector is apparently the calf, it is not yet clear whether phage-type 20a has a definite ecological relationship with this animal.

J. M. Browne Kutschbach

1306. **Control of Staphylococcal Cross-infection in Surgical Wards: a Four-and-a-half-year Study**
W. A. GILLESPIE, V. G. ALDER, G. A. J. AYLIFFE, D. E. B. POWELL, and W. WYPKEMA. *Lancet* [*Lancet*] **1**, 1299–1303, June 17, 1961. 4 figs., 11 refs.

In this paper the authors report a study of staphylococcal cross-infection in 3 male surgical wards of the Bristol Royal Infirmary during 4½ years. Methods used to prevent cross-infection are evaluated.

During the control periods more than a third of all open wounds were infected with *Staphylococcus aureus*, much of the infection being detectable only by swabbing. Of the staphylococci, 87% were penicillin-resistant and most were resistant to one or more other drugs. The multiple-resistant staphylococci belonged to phage group III or to group I, including phage patterns 80 and 52/52A/80.

Infected urine, sputum, and discharging wounds were important sources of cross-infection. Nasal carriers of epidemic strains were also sources, though perhaps less important than open lesions. Nasal carriage by nurses was important in the operating theatre, less so in the

wards; staphylococci were probably transferred from patient to patient by contact with nurses' hands or clothing.

The precautions against sources were the prophylactic application of neomycin–chlorhexidine or neomycin–bacitracin cream to the noses of patients and chemoprophylaxis of open and drained wounds (which are particularly susceptible to infection) with a spray containing neomycin, bacitracin, and polymyxin or with powder and gauze containing chlorhexidine. The precautions against vectors were disinfection of bedding, baths and bathwater, urine bottles, crockery, nurses' hands, and ward barber's equipment.

Measures directed only against the sources were ineffective, presumably because open surgical wounds are not easily protected by antiseptics. But the simultaneous application of all the precautions reduced cross-infection of open wounds (especially by multiple-resistant staphylococci) to about one-third of its former incidence, and greatly diminished the incidence of other staphylococcal complications, including postoperative pneumonia.

The authors emphasize that no precautions can succeed unless they are applied thoroughly and with intelligent understanding of their purpose. Great care must be taken to see that all members of the staff, and particularly the nurses, appreciate the importance and purpose of the measures.

[This paper should be read in full by all surgeons, bacteriologists, and hospital "infection officers", together with the previous papers by these authors, to which full references are given.] *H. Caplan*

INDUSTRIAL MEDICINE

1307. Anosmia in Alkaline Battery Workers

R. G. Adams and N. Crabtree. *British Journal of Industrial Medicine* [*Brit. J. industr. Med.*] **18**, 216–221, July, 1961. 9 refs.

A study has been made at an alkaline battery factory of 106 men exposed at their work to 2 types of dust—cadmium powder, which contains 60 to 64% of cadmium oxide and 16 to 18% of ferrous iron; and nickel powder, which contains 72% of nickel hydroxide and 18 to 20% of graphite. A control group of 100 men was obtained from a neighbouring engineering works. The investigation consisted of 2 parts: (1) measuring olfactory acuity and recording the incidence of anosmia; and (2) macroscopic examination of the noses of the employees.

Olfactory acuity was assessed (*a*) by questioning the men about their sense of smell, and (*b*) by a modification of the Proets olfactometer, using phenol in liquid paraffin. The sense of smell of the battery workers was compared with that of 84 control subjects of similar ages. The results showed that significantly more battery workers had anosmia than the controls (15% to *nil*) and more also achieved poor results in the phenol smelling test (27·3% compared with 4·8%). Examination of specimens of urine demonstrated the presence of cadmium proteinuria in 17 of the battery workers, of whom 11 had virtual anosmia.

Examination of the noses of 85 battery workers and 75 controls demonstrated signs of non-specific chronic irritation more frequently in the battery workers, but no significant relationship between this finding and the presence of anosmia could be established.

Contamination of the atmosphere in the factory is controlled by exhaust ventilation. Estimations of the concentration of cadmium in the air at various sites in the factory have been made since 1957, and the latest readings (1960) show a reduction in the amount of cadmium, the concentrations ranging from 0·34 to 6·65 mg. per cubic metre of air. Estimations of nickel concentration showed readings considerably below those for cadmium.

The authors conclude that the anosmia in the cases studied is attributable to exposure to cadmium or nickel dust or to a mixture of the two, but they were unable "to discover which of the ingredients of the two powders is responsible". *R. G. Meyer*

1308. Ischemic Necrosis in Anthracosilicosis

P. A. Theodos, R. T. Cathcart, and W. Fraimow. *Archives of Environmental Health* [*Arch. environm. Hlth*] **2**, 609–619, June, 1961. 7 figs., 11 refs.

A study was undertaken at the Jefferson Medical College Hospital, Philadelphia, in order "to clarify the nature of cavitation in anthracosilicosis and its exact relationship to tuberculosis with the hope that the divergent views concerning the relationship could be reconciled". The study was based on the observation of 1,980 anthracite coal miners who, over a period of 13 years, had been admitted to hospital "primarily for evaluation of their silicosis and for physiologic study of the nature and degree of the cardiorespiratory impairment". When cavitation was observed a detailed history was taken and physical examination and appropriate x-ray and bacteriological investigations were carried out. The 24-hour volume of sputum was weighed in grammes. A smear of sputum was examined for tubercle bacilli, and if this was negative 2 more specimens were scrutinized and one cultured. Cultures were also obtained from one 24-hour concentrate, one 72-hour concentrate, and one aspiration of fasting gastric contents. When necropsy was performed cavity contents were examined for tubercle bacilli by smear and culture with subsequent histological examination of the area.

Definite cavitation was observed radiographically in 206 cases (10·4% of the 1,980 patients), being seen on first admission in 188 of these but only subsequently in the remainder. Acid-fast bacilli were found in the sputum by smear or culture in 141 cases (68·4%). [What proportion of positive results was yielded by each of these methods is not stated.] Of the remaining 65 cases, carcinoma accounted for cavitation in 2 and cystic bronchiectasis in 2, and the cause was uncertain in 4. Cavitation in the other 57 cases "seemed best explained by ischemic or aseptic necrosis"; this was unilateral in 37 cases and bilateral in 19, and in one case cavitation (bilateral) was found only at necropsy. Opening and closing of cavities was noted in 13 cases.

The authors discuss the pathology of ischaemic necrosis in "large conglomerate masses of anthracosilicosis"

[progressive massive fibrosis of British writers] in the light of the reduction of bronchial arterial supply within the masses and the thickening and endarteritis obliterans of these vessels on the one hand; and on the other the lack of inflammatory cells and tuberculous histology in the vicinity of cavities, failure to detect tubercle bacilli on section or by culture, and the raggedness of cavity walls. [The number of necropsies is not given.] From the clinical standpoint they found that men with cavities apparently of ischaemic type had little if any constitutional disturbance other than the periodic coughing up of a " copious amount of inky black material " and that such cavities appeared " benign ". It is pointed out that small areas of ischaemic cavitation not visible radiologically are " more common than clinically appreciated ", being found as they are at necropsy.

The authors state that their findings give " confirmation of the association of cavitation with tuberculosis in anthracosilicosis ".

[There is nothing in this paper that has not already been described in the extensive literature of South Wales authors, though little reference is made to it, and the important work of Kilpatrick and others (*Thorax*, 1954, **9**, 260; *Abstr. Wld Med.*, 1955, **17**, 510) and Rivers and colleagues (*Brit. J. industr. Med.*, 1957, **14**, 39; *Abstr. Wld Med.*, 1957, **22**, 70) on this topic is not referred to. The number of patients reported to have had tubercle bacilli in the sputum is remarkably high, and, as we are not told in detail how cases were selected and analysed, bias cannot be excluded. Furthermore, the criteria for identifying tubercle bacilli may not have been strict enough; and, in this respect, no mention is made of atypical or " anonymous " mycobacteria which may well have a significant association with progressive massive fibrosis.] *W. Raymond Parkes*

1309. **Pneumoconiosis and Respiratory Symptoms in Miners at Eight Collieries**

J. M. ROGAN, J. R. ASHFORD, P. J. CHAPMAN, D. P. DUFFIELD, J. W. J. FAY, and S. RAE. *British Medical Journal* [*Brit. med. J.*] **1**, 1337–1342, May 13, 1961. 7 figs., 28 refs.

This paper reports results from the Pneumoconiosis Field Research Scheme of the British National Coal Board in which the complete working population at a number of collieries has been examined radiologically and by measurements of ventilatory function. A brief questionary concerning respiratory symptoms was also completed for every employee. The eight collieries with which this paper is concerned were in Scotland, England, and South Wales, and 9,758 men were studied. The radiographs were classified according to the International Labour Organization (1953) Classification. The proportion of men with pneumoconiosis of Category 1 or more at the collieries ranged from 9·1 to 41%.

There was a small decline in forced expiratory volume with increasing radiological abnormality at all ages. Subjects with respiratory symptoms had a lower ventilatory capacity than those without respiratory symptoms, the absolute difference being very similar at all ages; but because of the decline with age the proportionate reduction was greater in the older men. There tended to be more respiratory symptoms at the collieries with the higher incidence of pneumoconiosis, and the proportion of men with respiratory symptoms increased with increasing radiological severity of pneumoconiosis.

It was also found that reduction in ventilatory capacity with respiratory symptoms was greater in men without pneumoconiosis than in those with pneumoconiosis. Various reasons for this association are discussed; it is suggested that there may be some interaction between liability to develop pneumoconiosis and liability to develop symptoms of bronchitis. It may be that those men who develop pneumoconiosis are more robust or perhaps the development of bronchitis may reduce the liability to retain dust in the lungs. *C. M. Fletcher*

1310. **Inhalation of Sulfur Dioxide: Comparative Behavior of Bronchiolar and Pulmonary Vascular Smooth Muscles**

H. SALEM and D. M. AVIADO. *Archives of Environmental Health* [*Arch. environm. Hlth*] **2**, 656–662, June, 1961. 5 figs., 9 refs.

At the University of Pennsylvania, Philadelphia, the effect of sulphur dioxide inhalations on bronchomotor tone and pulmonary vascular smooth muscle was investigated in dogs which were made to breathe sulphur dioxide in concentrations of 200 to 850 p.p.m. in atmospheric air. The amount of sulphur dioxide retained in the animal was determined in each experiment.

In 15 experiments on 10 dogs inhalation of the gas produced bronchiolar dilatation followed by constriction, though in 3 instances only bronchodilatation occurred. Administration of atropine before exposure to sulphur dioxide produced irregular responses, but it seemed likely that the initial bronchodilatation was independent of the action of the vagus nerve. Pulmonary arterial pressure showed a variable response to sulphur dioxide. In 3 cases in which there was no bronchomotor response the pulmonary arterial pressure rose, suggesting that the pulmonary vessels are more sensitive to sulphur dioxide than the bronchioles. The pulmonary blood flow did not change during the rise in pulmonary pressure, suggesting that the latter must be due to vasoconstriction rather than to increased blood flow. Administration of atropine had no effect on vasoconstriction, which was thought to be a direct effect of the sulphur dioxide. *W. K. S. Moore*

1311. **The Question of Pulmonary Emphysema in Players of Wind Instruments.** (Zur Frage des Lungenemphysems bei Blasinstrumentenspielern)

K. REJSEK, M. NAVRÁTIL, and J. GLÜCKSMANN. *Archiv für Gewerbepathologie und Gewerbehygiene* [*Arch. Gewerbepath. Gewerbehyg.*] **18**, 343–348, 1961. 2 figs., 11 refs.

At the Institute for Occupational Diseases, Prague, 88 professional players of wind instruments were subjected to clinical, radiological, and electrocardiographic examination. In 84 cases residual air was measured and vital capacity estimated. By means of a modified lumbar-puncture needle inserted at the corner of the mouth and

connected to a mercury manometer the intra-oral pressure was also measured while the subject played his instrument. The results were not strictly comparable as they varied with the player's age, instrument, and technique of playing, while intra-oral pressures varied particularly with the position of the tongue. They are therefore presented with reference to the instruments played, these being grouped into brass, wood-wind, and flutes and piccolos; the mechanics of respiration while playing each group are described. The players are also grouped according to age and length of musical career, while intra-oral pressures are given as recorded during the playing of each instrument *piano*, *mezzoforte*, and *forte*.

Of the 84 musicians so tested, the vital capacity was normal in 8, reduced in 19, and raised in 57. Clinically, emphysema was present in 5 players, but 3 of these were over 50 years of age and all 5 had chronic bronchitis and were heavy smokers. Further, only 4 of them had an increased residual volume so, strictly speaking, only 57 of these wind-instrument players had proven emphysema.

D. Goldman

1312. **The Kidney in Lead Poisoning**

Z. RADOŠEVIĆ, M. ŠARIĆ, T. BERITIĆ, and J. KNEŽEVIĆ. *British Journal of Industrial Medicine* [*Brit. J. industr. Med.*] **18**, 222–230, July, 1961. 2 figs., bibliography.

The authors, at the Institute of Medical Research, Zagreb, have studied the renal changes produced by lead poisoning. In 44 (40 men and 4 women) of the 53 patients studied the lead poisoning was due to occupation and in 9 (5 men and 4 women) to the domestic use of lead-glazed pottery. The duration of exposure varied from 2 months to 35 years. The diagnosis of lead poisoning was based on clinical observation and the results of laboratory tests; the investigation included determinations of stippled cells and reticulocytes and the blood lead and urinary porphyrin levels; urine analysis in the urine concentration test, phenol red test, and urea clearance test; determinations of blood urea; and measurements of blood pressure.

The results of this investigation demonstrated permanent changes in the form of chronic nephropathy in only 2 patients who had experienced the longest and most intense exposure to lead; 23 patients showed functional renal lesions which tended to become normal. In addition to the patients with organic nephropathy, one other patient had a persistently raised blood pressure; in 2 cases an increase in blood pressure was observed only during the acute stage of poisoning.

The authors conclude that lead intoxication can give rise to renal lesions which are mainly functional and temporary. It seems possible that organic renal lesions can be caused by long and severe exposure and by repeated lead intoxication. The authors ascribe the disturbances of renal function which they observed to disorder of the intrarenal circulation caused by the spastic effect of lead on the intrarenal blood vessels and to a direct toxic or indirect hypoxic effect of lead upon the tubules. It was observed during the investigation of renal function that the timing of individual tests is of the greatest importance; some lesions may undergo changes during the natural course of lead poisoning, and if this fact is not borne in mind apparently contradictory results may be obtained.

R. G. Meyer

1313. **Trithion Poisoning**

C. E. D. HEARN. *British Journal of Industrial Medicine* [*Brit. J. industr. Med.*] **18**, 231–233, July, 1961. 6 refs.

The author reports 19 cases of poisoning by the organophosphorus insecticide "trithion" (0:0-diethyl S-*p*-chlorophenylthiomethyl phosphorodithioate) occurring among workers on a sugar-cane estate in Trinidad. There were 535 workers at risk, of whom 60 worked in the mixing-shed; the others applied the 2% dust, by means of dusting-guns, to the soil at the base of the sugar-cane stool. The determinations of whole-blood cholinesterase values were made by the rapid field method, using a Lovibond "comparator" and portable field kit; the blood samples were taken and estimated in the clinic, and not in the field, to avoid contamination of reagents by drifting dust. There were no fatalities. Out of 10 cases of trithion poisoning observed in 1959, 7 were mild and 2 moderately severe, requiring treatment with atropine. All the cases occurred among field workers, except one serious case in an East Indian employed in the mixing-shed; in this case the patient had been attacked by some of his colleagues and trithion dust forced into his mouth. The next morning the man presented with nausea, vomiting, severe abdominal colic, excessive sweating, salivation, pallor, apprehension, restlessness, headache, ataxia, and fine fibrillary tremors of the lids and face. Treatment with repeated doses of atropine over 30 hours resulted in complete recovery.

The investigation emphasized the difficulty of applying adequate safety precautions, as protective equipment is not readily tolerated by the workers. Those engaged in the mixing-shed work in well-ventilated and relatively cool surroundings and do not undergo arduous physical exertion. The conditions in which the field workers are employed, on the other hand, produce a marked peripheral vasodilatation, rapid subcutaneous blood flow, and increased respiratory exchange—factors which facilitate absorption of the insecticide adhering to the skin, while the quantity inhaled may be considerable. The author emphasizes that constant vigilance and the use of the portable field kit make it possible to detect exposure before serious poisoning develops. Observation of the patients in the present study showed that none of them developed any delayed neurological lesions.

R. G. Meyer

1314. **Psychiatric Sequelae of Chronic Exposure to Organophosphorus Insecticides**

S. GERSHON and F. H. SHAW. *Lancet* [*Lancet*] **1**, 1371–1374, June 24, 1961. 17 refs.

The authors, from Prince Henry's Hospital, Melbourne, describe schizophrenic and depressive reactions observed in 14 men and 2 women working in fruit-growing districts. The possibility that the mental disorders might be due to exposure to organophosphorus insecticides is discussed; but satisfactory evidence of a causal relationship was not obtained.

Derek Richter

Forensic Medicine and Toxicology

1315. **The Application of the Gm System in Paternity Cases.** [In English]
M. HARBOE and J. LUNDEVALL. *Vox sanguinis* [*Vox Sang.* (Basel)] **6**, 257–273, May, 1961. 1 fig., 48 refs.

The authors present from Rikshospitalet, Oslo, a survey (with an exhaustive bibliography) of the work done on the gamma-globulin (Gm) blood group system in which haemagglutination-inhibition reactions with selected " rheumatoid " sera are used to divide test sera into groups showing a genetically determined inheritance pattern. Following the nomenclature suggested by Eyquem *et al.* (*Nature* (*Lond.*), 1961, **189**, 845) the occurrence of the phenotypes Gm (a+), Gm (b+), Gm (x+), and Gm (x−), their incidence and pattern of inheritance as found in large samples of the Norwegian population, and their probable genetic relationships are fully discussed, while a number of minor recently discovered gamma-globulin factors at present under investigation are mentioned. An account is also given of reagents and technical methodology, with a section drawing attention to the errors likely to arise in grouping blood from infants under the age of 8 months and persons suffering from hypogammaglobulinaemia. In addition the effects of heating test sera up to 63° C. for 15 minutes, and of storing them at room temperatures for up to a week, are considered; it is concluded that, providing certain precautions are observed, no harm results from these procedures.

Finally, a short assessment, based upon the phenotype and gene frequencies found in the Norwegian population, of the use of this system in cases of disputed paternity is made in which it is stated that the mean chance of exclusion of paternity, using anti-Gm^a, anti-Gm^b, and anti-Gm^x is as high as 27%. The authors consider that this system should thus prove to be a valuable new tool for the forensic serologist and conclude with a plea for the extension of family studies in this field.

Gilbert Forbes

1316. **The Interpretation of the Surface Pattern of Vehicular Injuries**
K. SIMPSON. *Medicine, Science and the Law* [*Med. Sci. Law*] **1**, 420–428, July, 1961. 9 figs.

The author begins this paper by emphasizing the importance of correctly interpreting surface injuries caused by vehicles in the light of the known circumstances of the accident, illustrating this point by a few apt examples. He then briefly discusses the types of injury caused by initial vehicular impact and those subsequently incurred before the body comes finally to rest. Stress is laid on the need to consider the physique of the victim together with the " impact area " of the vehicle concerned, and other factors such as the protective effect of clothing and headgear, before arriving at any conclusion regarding the probable sequence of events. Excellent illustrations are given of characteristic injuries caused by sliding and falling upon various types of surface as well as by crushing and by direct impact. *Gilbert Forbes*

TOXICOLOGY

1317. **Has Thalidomide (" Contergan "; " Distaval ") No Ill Effects?** (Bewirkt Thalidomid (Contergan) keine Schäden?)
H. J. RAFFAUF. *Deutsche medizinische Wochenschrift* [*Dtsch. med. Wschr.*] **86**, 935–938, May 12, 1961.

Thalidomide, a hypnotic drug free from barbituric acid, has been considered to be harmless even on prolonged medication and in high dosage. The history of 14 patients seen during the last year at the Municipal Neurological Clinic, Essen, and here described, has established the fact, however, that this drug may produce severe neurological side-effects. These take the form of sensory disturbances in the hands and feet, a very irksome and at times intolerable prickling, and " pins and needles " paraesthesiae with numbness starting in the tips of the fingers and toes and extending over the glove and stocking areas. The feet feel as if they were " going to sleep " and the skin feels sandy or furry. The reflexes may be normal, but there is sometimes a diminution or loss of the Achilles tendon and patellar reflexes. In a few cases there was some degree of ataxia, both in gait and in accuracy of aim, while in others obstinate constipation developed. There was no abnormality in the cerebrospinal fluid, blood picture, sternal marrow, liver function, or gastric secretion. In patients who had been taking 100 to 200 mg. of the drug nightly for a year or more subjective improvement began only 3 to 4 months after the drug had been stopped, but even then the neurological findings remained unaltered. A case illustrating this condition is described in detail.

All 14 patients, men and women over 40 years of age, belonged to the middle or higher social classes, which are most troubled by insomnia. One had taken thalidomide for 3 weeks only and another for 5 weeks, but the remainder had been taking it for 6 months or longer. Only one had an initial skin reaction thought to be allergic, but the symptoms subsided in the course of weeks in spite of continued use of the drug. When thalidomide has been taken for a few weeks only and then stopped there may be a swift regression of the symptoms. The author describes the case of a medical student who had been taking 100 to 150 mg. of the drug nightly for some 3 or 4 months while preparing for an examination. Towards the end of his examination he suffered unbearable paraesthesiae in the finger tips and feet. During the vacation he stopped taking the drug

and after a few days paraesthesiae vanished completely. A few months later he again took thalidomide for insomnia, but after a few days the pain returned in his hands and feet. Again he stopped the drug—and the symptoms once more disappeared.

It is emphasized that one must be chary of attributing these serious neurological effects to a simple allergic sensitization. The possibility of addiction is discussed and one case described in which a state of euphoria, rather than sedation, was induced in a woman who sought treatment for alcoholism. Pending further investigation, it is advised that this drug be withheld from patients with any disease of the digestive system, liver damage, or cardiovascular disease. One woman suffering from infective hepatitis took 100 to 125 mg. of thalidomide daily for only 3 days for the relief of pain, and thereafter she fell into an acutely delirious psychotic state. More than 20 cases of these neurological side-effects of prolonged thalidomide medication are known to the author, who stresses that the effect is not that of harmless fleeting paraesthesiae but of a severe neurological disturbance which may persist for a long time after withdrawal of the drug. *M. A. Dobbin Crawford*

1318. **Polyneuritic Syndrome after Prolonged Medication with Thalidomide.** (Polyneuritische Syndrome nach längerer Thalidomid-Medikation)
W. Scheid, H. H. Wieck, A. Stammler, A. Kladetzky, and E. Gibbels. *Deutsche medizinische Wochenschrift* [*Dtsch. med. Wschr.*] **86**, 938–940, May 12, 1961.

Writing from the University Neurological Clinic, Cologne, the authors state that thalidomide (" contergan forte ", containing 100 mg. of thalidomide in each tablet) enjoys a special reputation as a useful hypnotic free from barbiturate. Clinical observation has now confirmed, however, that the use of this drug even in prescribed dosage, and not only in excessive dosage, can lead to a severe polyneuritic syndrome and 9 such cases occurring in 7 women and 2 men, all but one aged 45 or over, are described.

The symptoms may appear after taking thalidomide in a dosage as low as 50 mg. daily for 3 months. Occasionally the interval may be longer, even with a larger dose; thus one patient, a woman aged 61 had been taking 200 to 300 mg. of the drug daily for 18 months before any side-effects were noted. The symptoms begin with a loss of sensation or numbness, which is not always strictly symmetrical. There is a complaint of " pins and needles " in the extremities and a feeling of constriction and tension in the legs and feet, which may also be accompanied by a burning and prickling pain. In this series investigation invariably revealed a sensory disturbance, of which diminution or loss of sensation was a constant feature, though occasionally there was hypersensitivity. The area affected corresponded with the area of numbness; the lower limbs were always affected and generally also the upper limbs, and commonly on the inner aspect of the glove and stocking regions, but in one exceptional case the instep was affected, and in 3 others the abnormal sensation lay in a horse-shoe pattern on the inner side of the hand, a distribution which has also been observed in diphtheritic polyneuritis. In only one case was there a slight impairment of deep sensation.

Following the sensory disturbance, a motor defect may develop. In 2 cases there was a discrete paresis of the foot and toe extensor muscles and in one a weakness of the flexors of the toes; also in 2 cases there was weakness of muscle groups taking origin from the pelvis and these patients complained of difficulty in climbing steps and in rising from their knees. With the paralysis there was a diminution or loss of the Achilles tendon and patellar reflexes. A definite paralysis of muscles of the upper limb was not found, and trophic injury was seen in one case only. The cerebrospinal fluid, examined in 2 cases, showed no abnormality.

While agreeing that a final pronouncement cannot be made on the evidence of only 9 cases, the authors state that the polyneuritis is markedly persistent; in one of their cases it persisted without improvement for many months after the drug had been withdrawn. In the light of the clinical history of other forms of polyneuritis due to toxic substances it may be expected that the symptoms of thalidomide polyneuritis too should, in the course of time, completely disappear. In conclusion it is hoped that this report may contribute to the early diagnosis of thalidomide polyneuritis and avoidance of more serious injury. In the presence of any polyneuritic syndrome a close study of the aetiology is essential.
M. A. Dobbin Crawford

1319. **Coma Due to Massive Intoxication with Meprobamate, with Reference to 9 Personal Observations.** (Les comas des intoxications massives par le méprobamate (à propos de 9 observations personnelles))
P. Mollaret, J. Lissac, M. Goulon, J. J. Pocidalo, M. Rapin, and J. Chassigneux. *Bulletins et mémoires de la Société médicale des hôpitaux de Paris* [*Bull. Soc. méd. Hôp. Paris*] **77**, 504–511, 1961. 26 refs.

Nine cases are described in which an overdose of meprobamate caused complete coma lasting 10 to 45 hours according to dose, which ranged from 6·4 to 25 g. In all cases the corneal reflex was abolished; the condition of the tendon reflexes depended on the dose. In no case was there an extensor plantar reflex. In most cases there was a severe fall in blood pressure, rapid respiration, and a fall in arterial oxygen tension. The most effective treatment was by infusion of noradrenaline, which in some cases was maintained for 24 hours to a total dosage of 32 mg., combined with oxygen inhalation, after intubation if necessary. All the patients made a good recovery. *V. J. Woolley*

1320. **Treatment of Acute Experimental Carbon-monoxide Poisoning with Oxygen under Pressure**
D. D. Lawson, R. A. McAllister, and G. Smith. *Lancet* [*Lancet*] **1**, 800–802, April 15, 1961. 2 figs., 9 refs.

Investigations were carried out at the University of Glasgow on (1) the effect of increased oxygen pressure on rodents gassed with carbon monoxide; (2) the effect *in vitro* of exposure of carboxyhaemoglobin to air, oxygen,

and oxygen under pressure; and (3) the rate of removal of carbon monoxide from dogs which had been gassed with this substance and then exposed to air, oxygen, " carbogen ", and oxygen under pressure.

(1) Three groups each of 12 rats and 3 guinea-pigs were subjected to an atmosphere of 3% carbon monoxide in air in a chamber. Group A was kept as a control; the remainder were then exposed to oxygen, which was admitted to the chamber to a pressure of 15 lb. per square inch (1·054 kg. per sq. cm.) above atmospheric after the animals were unconscious (Group B) and simultaneously with the start of inhalation of carbon monoxide (Group C). Group-A animals died within minutes, whereas those of Group B recovered consciousness in one to 3 minutes and Group C remained normal. The authors suggest that in the animals which recovered a small but biologically significant amount of carboxyhaemoglobin was dissociated to yield more haemoglobin for oxygen carriage. Analysis of the heart blood of these animals immediately after their removal from the chamber showed that twice as much oxygen was carried by the haemoglobin in Groups B and C as in Group A.

(2) Six 20-ml. samples of human and equine blood were exposed to coal-gas and when equilibrated were subjected to air and to oxygen at various pressures. Carboxyhaemoglobin lost carbon monoxide slowly over a period of 50 minutes when filmed in air, faster in one atmosphere of oxygen, and most rapidly in 2 atmospheres of oxygen.

(3) Four dogs were caused to inhale carbon monoxide under anaesthesia. After 2 hours respiratory depression occurred, at which time artificial respiration was instituted. The animals were made to inspire air, carbogen (5% carbon dioxide+95% oxygen), or oxygen at one and 2 atmospheres' pressure at a flow rate of 6 litres per minute. The carboxyhaemoglobin content of the blood was determined throughout the experiment. It fell from 70% to 15% in just under 20 minutes during exposure to oxygen at 2 atmospheres' pressure; this took 40 minutes with carbogen and with oxygen at a pressure of one atmosphere. After 40 minutes air had reduced the carboxyhaemoglobin level by only 40%, and was thus the least effective agent.

After inhalation of carbon monoxide the carboxyhaemoglobin formed alters the dissociation curve of the remaining oxyhaemoglobin and so impedes oxygen release to the tissues, resulting in toxic and sometimes fatal effects, which oxygen given at 2 atmospheres' pressure prevents. This, the authors consider, is a logical form of treatment which they state has already been used successfully on persons poisoned with carbon monoxide.

Anne Tothill

1321. **Acute Collective Methyl Bromide Poisoning.** (Intoxication aiguë collective par le bromure de méthyle) J. Pernod, M. Tommasi, R. Damasio, J. Larribaud, and J. Magerand. *Bulletins et mémoires de la Société médicale des hôpitaux de Paris* [*Bull. Soc. méd. Hôp. Paris*] 77, 235–244, Nos. 7 and 8, 1961. 2 figs., 3 refs.

The clinical and pathological features of acute methyl bromide poisoning are described as seen in 13 soldiers who were exposed to the toxic vapour when using methyl bromide fire-extinguishers in an enclosed munition store. The signs and symptoms were roughly proportional to the period of exposure. In the most severe case, which proved fatal, the exposure had been for one hour without a mask. In this case, which is described at length, the early clinical features included initial loss of consciousness followed on recovery of consciousness by agitation and hiccup, giving place on the second day to somnolence and severe dysarthria. Neurological examination showed ataxia with hypertony of the lower limbs but not motor paralysis or signs of pyramidal involvement and the tendon reflexes were normal. Failure of neuromuscular coordination was marked, with adiodochokinesis and nystagmus. No sensory disturbances were found and the cranial nerves were not involved. Examination of the other systems showed nothing of note, but no urine was passed and 20 ml. of urine obtained by catheter contained much albumin. As the illness progressed the cerebellar signs improved, but the hiccups persisted with intermittent disturbances of consciousness until death on the 9th day. No abnormality of the optic fundi was observed. Respiratory signs developed, including paroxysms of dyspnoea requiring oxygen therapy, and later signs of pulmonary oedema appeared. The breath smelt strongly of methyl bromide for about 4 days. Adequate urine flow was never re-established and albuminuria was severe (2·5 to 3 g. per litre). The blood urea and potassium levels were increased. Post-mortem examination showed typical pulmonary oedema and evidence of toxic kidney damage, with severe degeneration of the convoluted tubular epithelium. Macroscopically, the brain was rather congested but not oedematous. Microscopically, lesions were found in the substantia nigra, red nucleus, olivary nucleus, cerebellum, and in the central grey nuclei. Detailed descriptions of these are given, the essential changes being intense vascular congestion with perivascular micro-haemorrhages and severe damage to nerve cells. The cerebral cortex and white matter were congested, but the nerve cells were well preserved. The pons was not involved.

In a further 4 less severe cases, in which exposure had lasted for about half an hour with the intermittent use of a mask, all the patients eventually recovered. In 3 of these there was loss of consciousness, immediate or delayed, inebriation, and vomiting, with later evidence of cerebellar involvement. The 4th victim showed inebriation and diplopia 3 hours after exposure, followed later by vomiting and giddiness. In the remaining 8 cases of mild intoxication the subjects had been exposed only by entering and leaving the munition store. In these the signs of poisoning were relatively minor and included vomiting, transitory inebriation, giddiness, tremors, hyperaesthiae, somnolence, transitory blindness, and anxiety. The authors emphasize that in the fatal case the patient never showed evidence of the abnormal muscular movements or clonic convulsions often reported by others. They also note that all their patients have shown various signs of nervous involvement several months after exposure, indicating the serious nature of the intoxication. A detailed account of the electroencephalographic investigations is given.

P. N. Magee

Anaesthetics

1322. **A Comparison of 3 New Synthetic Analgesics and "Demerol" as used for Preliminary Anesthetic Medication**
W. H. L. DORNETTE, M. F. POE, J. P. JONES, and B. H. HUGHES. *Anesthesia and Analgesia; Current Researches* [*Anesth. Analg. curr. Res.*] **40**, 307–313, May–June, 1961.

The authors of this paper from the University of Tennessee College of Medicine, Memphis, report that three new potent analgesics (designated Win 13,471, Win 14,098, and Win 16,516) were used for pre-anaesthetic medication in 179 patients and the results compared with those in 51 patients who received equipotent doses of pethidine. The drugs were administered intramuscularly together with 0·43 mg. of atropine about one hour before induction of anaesthesia. The anaesthetist assessed the patient's mental state and also pre- and post-operative analgesia.

In allaying apprehension without undue sedation Win 14,098 was found to be similar to pethidine. The three new drugs produced a variable change in blood pressure of a lesser degree than that produced by pethidine, but with all four narcotics there was often a fall in minute volume. Patients who received Win 13,471 frequently exhibited excessive salivation in the immediate post-operative period. The duration of anaesthesia was 5 to 6 hours with Win 16,516 and 4 to 5 hours with Win 14,098; but with Win 13,471 it was only 2 to 3 hours.
Mark Swerdlow

1323. **Evaluation of Fluphenazine Dihydrochloride (Prolixin) as a Premedicating Agent in Surgical Anesthesia**
J. F. ZEEDICK, G. J. THOMAS, A. L. PANTALONE, W. K. BUCHANAN, and D. J. BALTZER. *Anesthesia and Analgesia; Current Researches* [*Anesth. Analg. curr. Res.*] **40**, 323–327, May–June, 1961. 1 ref.

A trial of fluphenazine for premedication in surgical anaesthesia is described in this paper from the University of Pittsburgh School of Medicine and St. Francis General Hospital, Pittsburgh. Three dosage levels of fluphenazine were tried—0·015 mg. per kg. body weight, 0·03 mg. per kg., and 0·045 mg. per kg.—in nine groups, each of about 20 patients. The patients also received either atropine or scopolamine with or without pethidine. A control group of 22 patients received pentobarbitone, pethidine, and atropine. All the drugs were given by intramuscular injection except pentobarbitone, which was administered orally. Blood pressure and respiration and pulse rates were determined on the previous night and in the morning before medication. The mental state of the patient was assessed before the start of anaesthesia, assuming 5 degrees of sedation.

It was considered that less thiopentone was required for induction in the patients given fluphenazine than in the controls and that the reduction in the dosage of thiopentone was directly proportional to the dosage of fluphenazine. The amount of preoperative sedation was also proportionate to the dose of fluphenazine. There were no significant changes in blood pressure or respiration.
Mark Swerdlow

1324. **Preliminary Studies with AF 242 as an Antiarrhythmic and Preanesthetic Medication**
J. L. SCHMIDT, M. LOPEZ-BELIO, M. S. SADOVE, and O. C. JULIAN. *Anesthesia and Analgesia; Current Researches* [*Anesth. Analg. curr. Res.*] **40**, 362–367, May–June, 1961. 5 refs.

AF242 [1-(2-diethylaminoethyl)-5-ethyl-5-phenylbarbituric acid] affords significant protection in dogs against the ventricular fibrillation produced by ligation of the left circumflex coronary artery. The total average dose effective employed was 17 mg. per kilogram. During the course of anesthesia in man, AF242 injected intravenously in doses of 50 to 100 mg. aborted several cases of cardiac arrhythmia. In preliminary studies of AF242 as a pre-anesthetic medication, atropinic and sedative actions were noted. A combination of AF242 with meperidine was highly successful in controlling secretions in the upper respiratory tract during anesthesia.

AF242 deserves further study as a pre-anesthetic medication. It spares the blood pressure and should be investigated for use during heart surgery when ventricular fibrillation is threatened.—[Authors' summary.]

1325. **Anaesthesia for Neurosurgery with Sodium 4-Hydroxybutyrate in 220 Cases.** (220 cas d'anesthésie en neuro-chirurgie avec le 4-hydroxybutyrate de sodium)
G. LABORIT, A. KIND, and C. DE L. REGIL. *Presse médicale* [*Presse méd.*] **69**, 1216–1217, June 3, 1961. 6 refs.

This is a preliminary report of the use of sodium 4-hydroxybutyrate as the anaesthetic in 220 patients undergoing neurosurgery. This fatty acid, the toxicity of which is limited to a depression of respiration with massive doses, acts as a depressant, particularly on cardiac muscle. It has been used alone and combined with a neuroplegic agent, and also in performing artificial hibernation (30° C.), when it facilitated the attainment of hypothermia. Its muscle-relaxant properties permit intubation in the presence of spontaneous respiration, and in neurosurgery it prevents cerebral oedema by facilitating controlled respiration. Its hypotonic action on the heart, its bradycardiac effect, and the stable blood pressure accompanying its use make for safe anaesthesia. However, care must be taken to detect and control hypokalaemia, usually by administration of a potassium salt. This hypokalaemia must be compared with that associated with anabolic processes in general. It seems probable that sodium 4-hydroxybutyrate has a nitrogen-sparing action. Studies of this drug are continuing.—[From the authors' summary.]

Radiology

1326. **Differential Diagnosis of Intradural (Extramedullary) and Extradural Spinal Canal Tumors**
J. H. SHAPIRO, M. OCH, and H. G. JACOBSON. *Radiology* [*Radiology*] **76**, 718–732, May, 1961. 18 figs., 17 refs.

A review of 87 cases of intraspinal tumour (excluding intramedullary lesions) which have been studied by myelography is presented from the Montefiore Hospital, New York; all the tumours were confirmed histologically at operation or post-mortem examination. The cases are tabulated according to the microscopical diagnosis and age and sex incidence, while in addition the abnormalities detected on plain films are reviewed. The major part of the paper is devoted to the myelographic findings and to comparing and contrasting these findings in intradural extramedullary tumours with those of extradural tumours, with in addition a special study of the findings in meningiomata and neurofibromata. [The findings do not differ substantially from those of previous reviews of the myelographic changes of intraspinal tumours.]

The main points which are of value in the differentiation of intradural from extradural masses are as follows. (1) The position of the spinal cord; this is more often deviated by an intradural space-occupying lesion than by an extradural one, though it may be displaced by either. (2) The width of the subarachnoid space. Intradural extramedullary masses cause no separation of the column of opaque medium from the bony spinal canal and indeed the medium may be displaced towards the bony canal. In contrast, extradural masses commonly cause displacement of the opaque medium away from the margins of the bony canal, such displacement being most often seen in the frontal projection, but it may also be demonstrable in the oblique or lateral views. If the lesion surrounds the spinal canal a narrowing or tapering of the opaque column may be seen. (3) Intradural masses may show a filling defect or a partially radiotranslucent area in the opaque column. The filling defect is usually sharply defined, since the opaque material surrounds the mass except at its point of attachment. (4) The final observation of value in the differentiation of these two types of tumour is the contour of the opaque column when a complete block is present. Intradural extramedullary masses often present a deformity which is fairly characteristic, an eccentric, sharply circumscribed defect being seen. Also the margin is often cupped, the cup being formed by the opaque medium outlining one or other end of the polypoid mass. In comparison, the contour of the opaque medium in an extradural mass lesion most frequently shows a transverse serrated edge at the level of the obstruction.

It is concluded that an evaluation of the myelographic findings usually enables a differentiation between extradural and intradural tumours to be made. The importance of examining lateral as well as frontal views is stressed. *Arnold Appleby*

1327. **Retrograde Brachial Vertebral-basilar Angiography: an Analysis of Angiographic Visualization of the Vertebral-basilar System and Branches**
A. Z. OSTROWSKI, W. G. HARDY, D. W. LINDNER, L. M. THOMAS, and E. S. GURDJIAN. *Archives of Neurology* [*Arch. Neurol.* (*Chicago*)] **4**, 608–616, June, 1961. 7 figs., 16 refs.

Because of increased interest in the evaluation of extracranial occlusive lesions causing the stroke syndrome the study of both carotid and both vertebral vessels in the neck has been found desirable. In this paper from the Wayne State University College of Medicine and the Detroit Memorial and Grace Hospitals, Detroit, the authors discuss their findings in the first 90 cases studied by 4-vessel angiography. The patients included 28 in whom carotid artery disease was the primary clinical diagnosis. These patients had unilateral focal abnormalities of motion and sensation, or both, with or without dysphasia or aphasia. Many had recurrent focal neurological episodes with weakness or paralysis (including speech abnormalities) lasting for an hour or less. In 35 patients vertebral-basilar artery disease was suspected on the basis of a history of dizziness, diplopia, tinnitus, homonymous visual defects, and cranial nerve dysfunction. In 20 others occlusive cerebrovascular disease was suspected as being diffuse and not well localized in either carotid or vertebral-basilar systems.

The technique consisted in exposing the brachial artery in the lower third of the arm and, after arteriotomy, inserting a 4-cm. 15-gauge metal cannula towards the heart. Both brachial arteries were cannulated simultaneously under general anaesthesia. Between 15 and 30 ml. of 50% sodium diatrizoate was injected, usually 2 injections in each arm for antero-posterior and lateral views. After the injection the cannula was withdrawn and the arteriotomy closed with cardiovascular sutures. Recently a percutaneous technique has been used, a 17-gauge spinal needle being introduced into each brachial artery at the antecubital fossa. The authors state that " about once in every 15 to 20 cases one or both vessels have to be exposed ".

Carotid visualization on the right side was possible in 75 of the cases. However, by this technique the origin could not be seen in more than one-third of the group. The left carotid artery was seen very infrequently. The vertebral artery was found to be measurably narrowed at its origin in 38 cases. The left vertebral artery was larger in 40 cases, and the right in 34. There was non-visualization of the vertebral artery 4 times more frequently on the left side than on the right. In cases of occlusion of the origin of the vertebral artery evidence of collateral circulation was seen in a little over one-half of the cases. In two-thirds of these there was filling of the ipsilateral posterior cerebral artery from the carotid injection. Non-filling of the intracranial portion of the vertebral artery was usually interpreted as being " an

artefact if it was on the side of the smaller vertebral artery and if the basilar artery filled from the opposite larger vertebral side".

It is suggested that retrograde brachial angiography is safer than percutaneous subclavian angiography. Pneumothorax is avoided and positioning of the head is easier. *J. MacD. Holmes*

1328. **Blind Ductus Arteriosus**

P. KERLEY and B. STRICKLAND. *British Journal of Radiology* [*Brit. J. Radiol.*] **34**, 291–294, May, 1961. 9 figs., 4 refs.

In cases of congenital pulmonary stenosis a shallow bulge is often seen on the anterior wall of the pulmonary trunk, the bulge being due to the impact of the jet of blood. Again, in pulmonary stenosis and more often in Fallot's tetralogy a second anterior projection may be observed at the bifurcation of the pulmonary trunk; this has previously been attributed to a reflection of pericardium. The present authors consider that this appearance is due to filling of the blind end of the ductus arteriosus and discuss the angiocardiograms obtained in 3 cases of the tetralogy of Fallot and one of uncomplicated pulmonary valvular stenosis examined at the Westminster Hospital, London.

[Their view is certainly substantiated by the angiograms, which are reproduced.] *D. E. Fletcher*

1329. **Pulsations in the Pulmonary Arteries as Observed with Roentgenoscopic Image Amplification: Observations in Patients Having Increased Pulmonary Blood Flow**

B. B. GAY JR. and R. H. FRANCH. *American Journal of Roentgenology, Radium Therapy, and Nuclear Medicine* [*Amer. J. Roentgenol.*] **85**, 1025–1036, June, 1961. 5 figs., 10 refs.

The authors of this paper from the Emory University School of Medicine, Atlanta, Georgia, describe their observations on the pulsations of the pulmonary arteries in a group of 280 patients, using image amplification. In 90 of the patients there was increased pulmonary blood flow due to congenital heart disease with left-to-right shunts, but pulmonary arterial pressure was normal or only slightly elevated (less than 26 mm. Hg mean pressure). From these observations and the chest radiographs the pulmonary blood flow and pulmonary arterial pressure were predicted and checked with the findings at cardiac catheterization.

On the basis of the ratio of the pulmonary blood flow to systemic blood flow, the 90 patients who had increased pulmonary blood flow (due to atrial septal defect in 50, to ventricular septal defect in 35, and to patent ductus arteriosus in 5) were divided into 2 groups. In the first group, where the ratio was greater than 2, there were 49 patients, mostly those with atrial septal defects; all except 2 showed abnormal pulsation and the pulsation was equal on the two sides in 40 patients. The second group, with a ratio less than 2, contained 41 patients, most of them having ventricular septal defects; 14 showed normal and 23 asymmetrical pulsation.

In general the greater the pulmonary:systemic blood-flow ratio, the more obvious the radiological changes, and for equal pulmonary blood flow patent ductus, where the flow is distributed during systole and diastole, will produce less marked changes than septal defects, where there is only a systolic flow phase. The visible pulsation in these cases is probably related to the increased stroke volume of the right ventricle, and anatomical variations in the vessel wall are of little importance in this respect.

In 8 out of 9 cases studied postoperatively there was marked diminution in pulsation in branches of the right pulmonary artery, although little change occurred on the left side compared with the preoperative assessment. On the postoperative radiograph the vascularity pattern decreased, mainly due to the pulmonary veins returning to normal. *Michael C. Winter*

1330. **Pulmonary Veins in Congenital Heart Disease in the Adult**

R. S. ORMOND, A. K. POZNANSKI, and A. W. TEMPLETON. *Radiology* [*Radiology*] **76**, 885–893, June, 1961. 15 figs., 8 refs.

Four major venous channels are constant in position and can usually be identified in routine postero-anterior radiographs of the chest; they are the posterior division of the superior pulmonary veins, the superior and inferior divisions of the inferior pulmonary veins, and the middle pulmonary veins. These vessels can be seen crossing the arterial channels and entering the left atrium below the main pulmonary arteries. Postero-anterior films are best made in the 120 to 150-kV. range. In normal individuals the size of the veins varies considerably; with experience the subjective impression of vein size is quite useful. In congenital heart disease the veins in the lower lung fields are better correlated with blood flow, while in acquired heart disease the upper-lobe veins are better correlated with left atrial pressure.

In a study of the pulmonary veins at the Henry Ford Hospital, Detroit, Michigan, 6 normal subjects and 80 patients with congenital heart disease were examined. Of the latter, 22 had pulmonary stenosis, 27 interatrial and 13 interventricular septal defects, and 18 patent ductus arteriosus. Right heart catheterization was performed in all cases, with determination of intracardiac, pulmonary arterial, and pulmonary wedge pressures. The oxygen saturation of the blood in the heart and pulmonary artery was determined at suitable levels. The Fick principle was used to determine cardiac output and volumes of shunt when present. Ten of the patients had undergone selective angiocardiography, and the diagnosis was confirmed by surgery or at necropsy in 43.

In severe pulmonary stenosis the veins were found to be slender, while in less severe cases they were normal. In uncomplicated interatrial septal defect the pulmonary veins were considerably increased in size, the enlargement persisting in the presence of pulmonary hypertension. The veins in uncomplicated patent ductus arteriosus with left-to-right shunt were large, and the greater the shunt, the greater their size. When pulmonary hypertension was present the veins were large so long as a significant shunt persisted. With a balanced or reversed shunt they were smaller than in the other groups

and often smaller than normal. In interventricular septal defect the veins were of normal size if shunts were small, but increased in size in the presence of large shunts. When there was pulmonary hypertension the veins were large so long as the shunt persisted.

It is concluded that, since a successful surgical result in patients with pulmonary hypertension depends on the presence of a significant left-to-right shunt, " vein size offers one more method of evaluating the amount of such a shunt ". *John H. L. Conway-Hughes*

1331. **The Use of Intracardiac Carbon Dioxide in the Diagnosis of Pericardial Disease**
J. H. PHILLIPS JR., G. E. BURCH, and R. HELLINGER. *American Heart Journal* [*Amer. Heart J.*] **61**, 748–755, June, 1961. 9 figs., 5 refs.

This report from the Charity Hospital, New Orleans, Louisiana, confirms and supports previous work demonstrating the safety and diagnostic value of intracardiac injection of carbon dioxide in negative contrast radiography. Its greatest value has been in differentiating myocardial dilatation from pericardial disease and effusion. The technique is as follows. The patient is placed in the left lateral decubitus position in front of a 14 by 16 inch (35 by 40 cm.) film. The antecubital vein is punctured with an 18-gauge needle attached to a plastic extension tube and a 20-ml. syringe filled with 0·85% sodium chloride, the needle being kept open by periodic injections of saline. A film for comparison may be exposed at this stage, preferably during a moderately deep inspiration. A 50- or 100-ml. syringe is attached to a three-way stopcock, tested for airtightness, and then connected to a cylinder containing carbon dioxide. The connexions are " washed " several times with carbon dioxide gas by repeatedly filling and emptying the syringe, and the whole is then attached to the extension tube after removal of the 20-ml. syringe. The required amount of gas, usually 50 ml., is then injected rapidly, and films are taken immediately and at 4, 8, and 15 seconds after completion of the injection. The patient must be kept in the left lateral position for at least 10 minutes to ensure absorption of the gas from the right atrium.

The authors have used this procedure 36 times on 25 patients and found it to cause no distress to the patient. They state that there are few contraindications. The most important is in patients with intracardiac shunts because of the danger of coronary or cerebral embolism if gas should reach the left side of the heart, but this is very unlikely in the left lateral position. Again, patients with severe emphysema may not be able to excrete the gas, and patients with marked orthopnoea may be unable to maintain the lateral position long enough. Emphasis is laid on the need to ensure that the carbon dioxide used is pure.

Several " patterns " may be recognized radiographically after intravenous injection of carbon dioxide, and these are described. For instance, in myocardial dilatation the right atrial wall shows little if any change in width. Where there is free pericardial effusion the right atrial wall is widened; this may also be seen in acute or chronic pericarditis, but the widening is not usually so great and other clues may help to distinguish it. A note of warning is sounded in interpreting the radiograph in a case of right pleural effusion. When the patient lies in the left lateral position the fluid may gravitate down over the right cardiac border and simulate intrapericardial effusion. In such a case the carbon dioxide study must be postponed until the fluid disappears spontaneously or is removed by thoracentesis.
John H. L. Conway-Hughes

1332. **Modified Percutaneous Catheterization (after Seldinger) for Aimed Aortography.** (Abgewandelte perkutane Kathetermethode (nach Seldinger) zur gezielten Aortographie)
H. ZIMMERMANN. *Fortschritte auf dem Gebiete der Röntgenstrahlen und der Nuklearmedizin* [*Fortschr. Röntgenstr.*] **94**, 784–788, June, 1961. 5 figs., 9 refs.

The essential feature of the author's modified method of performing percutaneous catheterization for aimed aortography is that his catheter has a closed end with two lateral holes. The advantage is that by this device he obtains something like a selective bilateral renal angiogram, provided the catheter is introduced to the proper level opposite the origin of the renal arteries. The method has the comparative simplicity of aortography with the advantage of a practically selective bilateral renal angiogram. This method also differs from that of Seldinger in that a rather larger cannula is used for the puncture and both guide wire and catheter are within it; the result is that on withdrawal there seems to be less bleeding than with the Seldinger method. The main advantage gained by having two lateral holes at the end of the catheter is that the contrast agent is not propelled with such great force towards the higher level of the origin of the coeliac axis and the superior mesenteric artery. *F. M. Abeles*

1333. **Radiologic Localization of the Esophageal Hiatus as Determined by Intraluminal Pressure Measurements**
B. S. WOLF and B. R. COHEN. *Radiology* [*Radiology*] **76**, 903–910, June, 1961. 8 figs., 23 refs.

The x-ray shadow of the diaphragm is projected by rays tangential to the dome-shaped boundary between muscle and translucent lung. In so far as the oesophageal hiatus lies in the mediastinum it is impossible for it to cause a shadow. Neglect of this radiological platitude is probably responsible for some of the fantastically high estimates of the frequency of hiatus hernia. In the present paper an accurate method of locating the oesophageal hiatus from intraluminal pressure curves is described which confirms much other evidence that in the right-oblique position used following a barium drink the hiatus in normal subjects lies well above the shadow of the diaphragm.

Originally three and later six 3-ft. (91-cm.) lengths of polyethylene tube (internal diameter 1·4 mm., external diameter 2 mm.) were taped together and the ends sealed. For each tube a single lateral opening 3 mm. in length and half the circumference of the tubing was made just above the tip, and radiological identifica-

tion was made possible by fixing a silver clip to its lower margin. The tubes were so tied together that there was a distance of 1 cm., later reduced to 0·5 cm., between each opening. The apparatus was then arranged under x-ray screen control so that some of the openings lay in the oesophagus above the diaphragm and some below. The tubes were perfused with water at a " constant pressure and flow rate ", and by means of capacitance electromanometers pressure tracings were recorded; at the same time by means of a pneumograph belt respiration was recorded. In most instances clear-cut opposite excursions were obtained from two adjacent openings 1 cm. apart and it was then assumed that the level of the physiological hiatus lay midway between them. In some cases a diphasic tracing was obtained from one of the openings with opposite deflections from the openings above and below. In this type of record it was assumed that the hiatus was at the level of the opening producing the diphasic record. Tracings were obtained before, during, and after the taking of radiographs while the patient drank dilute barium through a wide-bore straw continuously or intermittently. The results in 10 normal persons were consistent; they indicated clearly that during drinking and during inspiration the hiatus lies at the junction of the phrenic ampulla with the narrow empty segment, which lies entirely within the abdomen. The sphincteric pressure segment lies partly above the hiatus and partly below. *Denys Jennings*

1334. **The Localization of Portal Obstruction by Splenoportography**
I. BERGSTRAND. *American Journal of Roentgenology, Radium Therapy, and Nuclear Medicine* [*Amer. J. Roentgenol.*] **85**, 1111–1119, June, 1961. 16 figs., 14 refs.

Recent experience with splenoportography has shown that the exact site of an obstruction in the portal venous system is often difficult to determine and in some cases the examination may give an incorrect indication of the site of a block. The obstruction may be directly visualized, but a false picture can be caused by reversed flow in the portal or splenic veins so that a patent portion of a vein will not be filled by the contrast medium. A block may be inferred from the development of a collateral circulation, which, in the case of intrahepatic obstruction, tends to be " hepatofugal " (away from the liver towards the systemic veins) and in extrahepatic obstruction " hepatopetal " (towards the liver into the portal vein beyond the block).

The author studied two groups of patients at the University of Lund, Sweden: (1) 91 patients with proved intrahepatic obstruction and (2) 19 with proved extrahepatic obstruction. Patients with obstruction at both sites were not included. The radiological appearances fell into five main groups. (1) Visualization of the splenic and portal veins with various types of hepatofugal collaterals but no hepatopetal collaterals was obtained in 85 cases of intrahepatic obstruction. (2) There was visualization of the portal vein via hepatopetal collaterals in 2 patients with splenic vein obstruction. (3) The splenic vein, non-filling of the portal vein, and hepatopetal collaterals were seen in most of the 12 patients with extrahepatic portal vein obstruction. (4) Non-filling of the portal and splenic veins with hepatopetal collaterals indicating obstruction in either the portal or splenic veins or both was visualized in 4 patients.

(5) In the final group, including less than 10% of the total, there was non-filling of the portal and splenic veins with only hepatofugal collaterals. The author states that this appearance indicates obstruction, but does not reveal its site; it may be caused by reversed flow or incomplete filling of some collaterals, and further examination during laparotomy is indicated in such cases.

Michael C. Winter

1335. **A Comparative Trial of Telepaque and Biloptin**
D. J. MANTON. *British Journal of Radiology* [*Brit. J. Radiol.*] **34**, 298–301, May, 1961. 5 refs.

There are now several satisfactory oral contrast media for cholecystography and it is very difficult to decide which to use as a routine. A comparative trial of " telepaque " (iopanoic acid) and " biloptin " (sodium ipodate) was carried out at Hammersmith Hospital, London, in 100 consecutive examinations, iopanoic acid being used in 49 and sodium ipodate in 51. It was found that sodium ipodate was slightly superior; although the degree of opacification of the gall-bladder was identical regardless of the contrast medium used, sodium ipodate caused fewer side-effects, particularly diarrhoea, than did iopanoic acid. The latter was found to outline the ducts after the fatty meal more often than did sodium ipodate.

[There is no mention of the frequency of appreciable quantities of media being unabsorbed and producing bowel shadows. Also it should be mentioned that many radiologists consider that both these media produce too dense a shadow, which may mask gall-stones or slight impairment of function.] *D. E. Fletcher*

RADIOTHERAPY

1336. **Grid Irradiation of Carcinoma of the Bronchus.** (Zur Siebbestrahlung des Bronchialkarzinoms)
H. G. SCHMITZ-DRÄGER, G. OBERHOFFER, and P. THURN. *Strahlentherapie* [*Strahlentherapie*] **114**, 481–500, April [received June], 1961. 5 figs., 39 refs.

This paper from the University Radiological Clinics of Bonn and Cologne, attempts to assess the relative value of grid therapy for bronchial carcinoma, as measured by the prolongation of life obtained. A total of 411 cases are reviewed, including 149 patients irradiated by grid techniques, 58 irradiated by other techniques, 36 treated by surgical resection, and 168 who received no radiotherapy; excluded from the study were all patients with adenocarcinoma, those treated with cytostatic agents or corticosteroids, those with severe concomitant disease likely to shorten life, and those whose survival time had not yet reached the average survival time of the patients who had died. To ensure that the groups were strictly comparable in regard to age, stage of the disease, and histology of the tumour a break-down into many subgroups was necessary. Unfortunately this resulted in the number of cases in each subgroup becoming

so small that statistical significance was difficult to obtain. However, it did emerge that grid therapy leads to the prolongation of life by an average of several months. The great advantage of the method in comparison with ordinary radiotherapy is the greatly reduced incidence of side-effects.

The authors conclude that radiotherapy is indicated as the primary treatment in the following conditions: (1) undifferentiated carcinoma in all stages; (2) differentiated carcinoma in Stages III and IV; (3) differentiated carcinoma in the earlier stages when for some reason operation is impossible; (4) occasionally, for symptomatic reasons, carcinoma in patients with distant metastases. The contraindications, such as very advanced disease, poor general condition or advanced age of the patient (over 70), and (rarely) the presence of a complication such as active tuberculosis, are also listed. The technique of grid therapy employed, which is fully described, included a lead–rubber grid (Pb equivalent 0·5 mm.) with circular holes 10 mm. in diameter, giving a total area of openings of 50%. Anterior and posterior fields were generally used and the daily dose in air was 1,000 r. In about half the patients a total air dose of 20,000 to 25,000 r. was possible, with a calculated tumour dose of 23% at 10 cm. *E. Stanley Lee*

1337. **Contribution to Pendulum Convergence Irradiation in Carcinoma of the Bronchus.** (Beitrag zur Pendelkonvergenzbestrahlung des Bronchialkarzinoms)
F. J. Hallermann and P. Jammers. *Strahlentherapie* [*Strahlentherapie*] **114**, 501–507, April [received June], 1961. 3 figs., 21 refs.

This paper reports the authors' experiences with combined pendulum–convergence-beam therapy for bronchial carcinoma of central type occurring in 87 patients treated at Knappschafts Hospital, Recklinghausen, Germany, between 1956 and 1959. Of these patients, of whom only 2 were women, 84 were available for follow-up evaluation. The cases were divided clinically according to the "T.N.M." classification of Wellauer and Maranta (*Fortschr. Röntgenstr.*, 1959, **91**, 555), who recognize 7 groups, namely, the usual Stages I to IV, plus non-involvement of lymph nodes (Na), involvement of lymph nodes (Nc), and distant metastases (M). Histological proof was obtained in only 15% of cases, but the tumour was verified by bronchography in 75%. Treatment factors included skin distance 50 cm., field size 6×9 or 6×13 cm., angle of arc ±150 degrees, and translational angle ±30 degrees. The daily tumour dose was 200 r. The aim was a 3-course treatment with 3 months' interval between the courses, with a total dose of 4,000 r. in each of the first 2 courses and 3,000 r. in the 3rd. In the event only 19 of the patients received the full triple course, 25 a double course, and 40 one course only; 30 patients were given an additional 1,200 r. to the mediastinum by fixed posterior fields, but the results of such additional treatment were bad and the method was abandoned. Apart from this, treatment was well tolerated, even by patients with severe silicosis.

The average survival period for untreated cases was taken to be 5½ months, while that with fixed field therapy is, according to the literature, little better. In the present series the average survival time for all patients was 9·1 months, 3 surviving for 20, 23, and 43 months respectively. When classified by stages as described the survival periods were as follows: Stage I Na (12% of cases) 19 months (these cases were inoperable only because of silicosis); Stage I Nc (8%) 10·3 months; Stage II Na (15%) 11 months; and Stage II Nc (33%) 7·9 months. The authors consider that these results show a definite advance and are of the opinion that combined pendulum–convergence-beam therapy is a promising method. *E. Stanley Lee*

1338. **The Results of X-ray Treatment in Undifferentiated Carcinoma of the Thyroid**
M. I. Smedal and W. A. Meissner. *Radiology* [*Radiology*] **76**, 927–935, June, 1961. 5 figs., 4 refs.

In this paper from the Lahey Clinic and the New England Deaconess Hospital, Boston, the authors describe 44 cases of undifferentiated thyroid carcinoma, inoperable because of extension to the neck or mediastinum, treated by 2-MeV. radiation. Histologically, the tumours were subdivided into giant-cell, small-cell diffuse, small-cell compact, cuboidal cell, and mixed types. Of the 15 patients with giant-cell tumours, 5 had pre-existing thyroid nodules or goitre. Treatment was not standardized, but the authors consider that a tumour dose of 5,000 r. in 5 or 6 weeks is adequate for the small-cell compact carcinoma which is relatively sensitive to irradiation and less malignant than the other types. For small-cell diffuse and giant-cell carcinomata smaller fields can be used and a tumour dose of 6,000 r. given in the same time interval. The cuboidal-cell carcinoma is the most benign, both of the patients with this type of tumour surviving 5 years. Other patients surviving 5 years included one (out of the 15) with giant-cell tumour, one (out of 12) with small-cell diffuse carcinoma, 4 (out of 7) with small-cell compact tumours, and 2 (out of 8) with mixed types. *M. Sutton*

1339. **Gonadal Exposure Incident to Roentgen Therapy**
G. Kaplan, C. Collica, and S. Rubenfeld. *Radiology* [*Radiology*] **76**, 877–880, June, 1961. 6 figs., 11 refs.

The radiation dose received by the gonads during irradiation in various sites was studied in patients at the Veterans Administration Hospital, New York. The physical factors of the beam were 250 kV., 2·3 mm. Cu half value layer (H.V.L.), 200 kV., 1·1 mm. Cu H.V.L., focus–skin distance 50 cm. The gonad dose was measured by a condenser-type ionization chamber with a volume similar to that of adult gonads (187 ml.). It was found that there was little advantage in providing lead rubber protection of greater thickness than 0·5 mm. equivalent. There was, however, a definite reduction in gonad dose if lead rubber was used below as well as above the gonad area. The dose, as expected, decreased with increased distance between gonads and the centre of the treatment field and with decrease in the size of the field. Graphs are shown of gonad dose as a function of the treatment-field size, field–gonad distance, and H.V.L. *M. Sutton*